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Contents

An Enquiry Concerning the Rôle of Allergy, Immunity and Other Factors of Importance in the Pathogenesis of Human Tuberculosis. ARNOLD RICE RICH AND HOWARD A. MCCORDOCK..... 273

Program Of The Medical Society of the Johns Hopkins Hospital..... 425

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AN ENQUIRY CONCERNING THE RÔLE OF ALLERGY, IMMUNITY AND OTHER FACTORS OF IMPORTANCE IN THE PATHOGENESIS OF HUMAN TUBERCULOSIS[1,2]

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CONTENTS

I. Natural species resistance and susceptibility 275
II. Differences in the virulence of different strains of tubercle bacilli 276
III. Individual differences in resistance 276
IV. The nature of "virulence" 277
V. Acquired resistance 279
VI. The mechanism of acquired resistance.
1. The allergic reaction 280
2. The relation of allergy to immunity 284
VII. The mechanism of allergy 305
VIII. Fluctuations in allergy 309
IX. Effect on the bacillus of residence in the allergic, immune body 310
X. The relative importance of virulence, resistance, allergy and size of infecting dose in determining:
1. Whether progressive infection will result 311
2. The character of lesion which will result
a. Development of the tubercle 312
b. The occurrence of caseation 314
c. Fibrous tissue of the tubercle 316
d. The question of "specific tuberculous granulation tissue" ... 317
XI. The possibilities as to the final outcome of tubercle formation 318
XII. The possibilities as to the final outcome of the allergic, inflammatory reaction 318
XIII. The pathogenesis of miliary tuberculosis 320
XIV. The principles involved in the differences between the effects of tuberculous infection in the adult as contrasted with the child 324
XV. The pathogenesis of lesions of the lung 346
XVI. The pathogenesis of lesions of the meninges 371
XVII. The pathogenesis of exudative lesions of the serous cavities 378

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[2] Expenses of publication defrayed by the National Academy of Sciences.

During the past several years we have been engaged in an experimental and morphological study of the pathology of tuberculosis, in an attempt to analyze the processes which determine the various forms of tissue reactions which are met with routinely at autopsy in any unselected series of cases of this disease. Because of a lack of precise information regarding the interaction of resistance, allergy, size of infecting dose, virulence of bacillus, etc., we had come to feel little security in our interpretation of many tuberculous lesions, and our dissatisfaction was not lightened by the fact that different "schools" in different parts of the world interpret even the most familiar forms of the disease in diametrically opposed ways. We hoped that a minute comparison of lesions observed at autopsy with those produced experimentally under controlled conditions might enable us to understand better the various types of injury caused by the tubercle bacillus, and further, might clarify somewhat our understanding of the nature and effects of immunity in tuberculosis. We have worked over ground which has, in many places, already been traversed by numerous investigators, for we wished to have first-hand information regarding the facts upon which are based the various and conflicting generalizations concerning the fundamental principles of tuberculous infection which are current at the present time. We have amplified these studies by certain experimental and morphological attacks which have not heretofore been applied to the problem. There are many unsolved problems relating to tuberculous infection, and we wish to emphasize that wherever we deal with such matters in this paper in the only way in which we are able to do at present, *i.e.*, speculatively, our aim is to formulate the problems clearly and to stress the need for further work, rather than to urge the acceptance of this or that comfortable theoretical solution.

Our conclusions are based upon the results of the experimental infection of about a thousand animals by different routes with various amounts of different strains of tubercle bacilli, and upon a minute study of the tissues from two hundred autopsies on cases of human tuberculosis, the ages of the patients ranging from seven weeks to seventy-three years. We cannot, in the present paper, enter into the finer details of experiments, or record individual protocols of autopsies or experiments. We shall in each instance merely state the general

procedure, and the results which bear upon the question under consideration. As regards the measurement of dosage of bacilli in our experimental inoculations, we have used thin, moderate and heavy suspensions of bacilli, having had care only that undue clumping of bacilli was guarded against as far as possible by painstaking preparation of the suspension, which was always freed from larger clumps by means of one or of a combination of the procedures of centrifugalization and filtration through cotton or filter paper; and, furthermore, that in each experiment both the test and the control animals received an equal amount of the same suspension from the same syringe. More refined methods of quantitation were unnecessary for our purposes except in a few experiments.

During the progress of this work we have placed before ourselves a series of questions, the answers to which are necessary for an understanding of tuberculous infection. Some of these questions are independent of the matter of tissue reactions, but most of them are concerned with the explanation of the various types of lesions. In order to develop the subject clearly, and to avoid explanatory digressions as we proceed, we shall state our experience relating to each of these question, dwelling as briefly as possible upon matters in which our own experience merely confirms the general experience of others.

Since the factors of virulence of the organism and resistance of the host are of first importance in any consideration of tuberculosis, we wished to know at the outset certain matters pertaining to virulence and resistance.

I. NATURAL SPECIES RESISTANCE OR SUSCEPTIBILITY TO DIFFERENT TYPES OF TUBERCLE BACILLI

In common with other investigators we have found that different types of bacilli (human, bovine, etc.) affect a given animal species with different intensity. We have used in this work a standard virulent human bacillus (H_{37}), a standard human bacillus of low virulence (R_1), a standard virulent bovine bacillus (B_1), an avian strain, and a 'non-pathogenic,' acid-fast bacillus (timothy).[3] When rabbits are infected with moderate and equal doses of H_{37} and of B_1, those receiving the

[3] We wish to acknowledge our indebtedness to Dr. H. S. Willis for his kindness in placing his supplies of tuberculin and bacilli at our disposal.

bovine bacilli develop extensive and rapidly fatal lesions, while those receiving the human bacilli (which are, however, extremely virulent for guinea-pigs) may live indefinitely, and at autopsy show, at best, isolated, slight lesions. Thus the guinea-pig is susceptible to H_{37} and the rabbit resistant. Both are susceptible to B_1, the rabbit somewhat more so than the guinea-pig. This has been the experience of all investigators.

II. DIFFERENCES IN THE VIRULENCE OF DIFFERENT STRAINS OF THE SAME TYPE OF THE BACILLUS

If moderate and equal doses of H_{37} and of R_1 are given to different guinea-pigs, those infected with H_{37} invariably die of widespread tuberculosis, while those infected with R_1 practically never do. Indeed, the dose of R_1 may be increased to many times the lethal dose of H_{37} and still the disease will not spread progressively to a fatal termination. Here, then, is a difference in virulence in different strains of the same type of (human) bacillus; and this difference in virulence has nothing to do with species resistance or susceptibility, for any species which is susceptible at all to H_{37} will be correspondingly less so to R_1. This has been the experience of all investigators.

III. IS THERE ANY DIFFERENCE IN NATURAL RESISTANCE OR SUSCEPTIBILITY TO THE SAME BACILLUS IN DIFFERENT INDIVIDUALS OF A GIVEN ANIMAL SPECIES?

While we have not pointedly investigated this question we have been impressed by the fact that in any large series of animals of approximately the same size, inoculated with the same amount of any type of tubercle bacillus by any route, although in general the series will present a fairly uniform pathological picture after a given lapse of time, some animals show marked variations from the average, in the extent of lesions. While it is perfectly true, as Petroff points out, that irregular clumping of bacilli in the syringe may complicate the exact equalization of dosage, we believe that the individual variations which we have observed have been too striking to have been entirely explainable in that manner. It seems to us more probable either that natural resistance is developed to a different degree in different individuals of the same species, or that a rather standard degree of natural species

resistance becomes altered in individuals by uncontrollable conditions of nutrition and bodily wellbeing. That species resistance can be altered deliberately in individuals has been familiar enough since the experiments of Pasteur on anthrax, and variations in acquired resistance to tuberculosis are well know to occur in the human being during pregnancy and in the face of diabetes and other diseases. It is important to realize, furthermore, that if conditions which hamper the prompt development of acquired resistance are present at the time of infection, the consequent severity of infection may be erroneously interpreted as an instance of unusual individual susceptibility. Any of the conditions known to depress acquired resistance may also inhibit its development.

IV

Since there are, definitely, differences in the virulence of different strains of a given type of bacillus, and, just as definitely, natural species susceptibility and resistance to any single given strain: *In what, then, does "virulence" consist?*

It is possible to conceive that each type of bacillus (human, bovine, etc.) elaborates a chemically different kind of poisonous material, that a virulent bacillus elaborates more of its particular kind of poison than does an avirulent one, and that species are susceptible or resistant depending upon whether or not their tissues are chemically constituted so that they can be acted upon by the particular poison in question. It is true that there is some evidence that the tuberculins prepared from different types of bacilli have somewhat different antigenic properties (64); however, neither a true exotoxin nor a potent "endotoxin" has been yet obtained from any tubercle bacillus. The unsensitized animal is relatively unaffected by the broth filtrate or the extracts of any form of tubercle bacillus, even of types to which the animal is highly susceptible, and quite enormous doses of living virulent bacilli or of bacillary extracts may be injected directly into the blood stream of a normal susceptible animal without causing any appreciable acute symptoms. There is, therefore, no evidence that a particular animal species is naturally susceptible to the poison of a particular type of bacillus. As for the sensitized animal, that is a quite separate problem, but it is of obvious importance in this connection that tuberculin

extracted from bacilli toward which the animal is naturally resistant is nevertheless toxic to the point of death for that animal if it has been previously inoculated with these bacilli.)

It seems proper to regard "virulence" as merely the relative ability of the particular strain of tubercle bacillus under consideration to *grow* in normal individuals of an animal species which is naturally susceptible to the type from which the strain in question is derived. In dealing with bacteria which produce an exotoxin, we can, to a certain extent, dissociate virulence from the host factor, for certain strains of the same type produce the toxin and other strains do not. What we mean when we speak of a tubercle bacillus as "virulent," however, has, as far as we know at present, nothing to do with the amount or the quality of toxin which that bacillus produces, but only with the observation that that particular bacillus produces progressive, spreading lesions in the species in question; and this means that the bacillus not only can survive in that species, but that it can freely propagate itself, for extensive lesions are out of the question unless great numbers of bacilli can be produced. If the bacillus does live and grow freely in the body for any length of time, it will unfailingly produce damaging lesions, and we shall speak of it as a "virulent" bacillus, although the death of tissue is, as far as we know at present, referable more to the development of hypersensitiveness to the protein of the bacillus than to any toxin elaborated by the bacillus itself. That a sufficient number of bacilli is the only requirement for the production of lesions is evident from the extensive, typical tuberculous lesions which can be produced with a sufficient intravenous dose of even the "non-pathogenic" timothy bacillus. That these lesions do not progress beyond a certain point, but tend to regress and to disappear is a result of the recognized inability of this bacillus to continue to live and to propagate freely in the body.

We have seen that different strains of the same type of bacillus vary in their power to damage a given animal species, and that, conversely, different animal species vary in their susceptibility to a given type of bacillus. It becomes evident, therefore, that no consideration of virulence is possible without a consideration of the host. One has always to ask the question: "Virulent—*for what animal?*"; and the relative virulence of different strains of the same type can be tested

only upon an animal species which is naturally susceptible to that type. Since neither Lewis and Sanderson (68) nor ourselves have been able to detect any difference in the fundamental tissue reaction of the body to different tubercle bacilli, whether of high or of low virulence, whether of types to which the body in question is resistant or is susceptible, we may, in the lack of more precise information, broadly consider each animal body as a test-tube, containing a medium which, under the existing conditions of temperature, is either favorable or unfavorable to the growth of the bacillus in question. Natural species and individual resistance or susceptibility will thus depend upon the degree to which the previously uninfected animal body in question is able to satisfy the growth requirements of the particular tubercle bacillus under consideration. It is from such a viewpoint that we regard the fact, which we have observed in common with Baldwin and Gardner (1), that out of a large number of guinea-pigs simultaneously infected with the same dose of the same emulsion of the avirulent R_1 bacillus, an occasional one will develop widely disseminated lesions; for the most careful efforts have shown that the bacilli recovered from the animals in which the lesions progressed (*i.e.*, in which the bacilli propagated more abundantly) are in no way different in virulence from the original R_1 strain. The difference must have resided in the body of the animal in which the bacilli were able to grow. In the present state of our information, further speculation on the nature of virulence would be of little profit here.

V. ACQUIRED RESISTANCE TO THE TUBERCLE BACILLUS

We have repeatedly observed, in common with all who have investigated the matter, that an animal infected with a sub-lethal dose of tubercle bacilli becomes, after some days, protected against subsequent infection with much larger doses of bacilli than the animal could have originally tolerated. There are several facts worthy of mention in this connection:

(1) Resistance in rabbits and guinea-pigs may be acquired by infection with either virulent, or avirulent, human or bovine bacilli, regardless of the animal's native susceptibility to the infecting organism.

(2) Resistance so acquired will protect indiscriminately against subsequent inoculations of virulent human or virulent bovine bacilli,

regardless of the animal's original susceptibility to the organism of reinfection, *i.e.*, the resistance is not type specific.

Here again the simile of the test-tube may be applied. The "medium" which was originally favorable to the growth of tubercle bacilli becomes so changed after infection that they can no longer survive and propagate as well in it. This we shall discuss at greater length below.

We shall use here interchangeably the terms "acquired resistance" and "acquired immunity," for, as has been often observed, infected animals become only relatively immune. They can always be killed with progressive lesions by a dose sufficiently large, and although they may survive a small dose which would kill a control, with somewhat larger doses their resistance is evidenced only by a period of survival longer than that of similarly infected controls, and they die eventually from progressive tuberculosis.

It is stated by many writers that if the bacilli of the protective infection ever die out, acquired resistance also vanishes. We have no experiments bearing upon this point, nor has anyone else adduced satisfactory proof of it.

VI. WHAT IS THE MECHANISM OF THIS ACQUIRED RESISTANCE?

Opinions differ. Krause (10), Zinsser (5), most American and many European investigators believe that resistance acquired through infection is largely a result of allergy, which also appears shortly after infection. This idea has been widely accepted in all countries ever since it was clearly formulated by Römer. It will be well here to define in what sense we shall use the term 'allergy.' Throughout the literature great emphasis is placed upon the 'exudative' nature of the allergic reaction. The Koch phenomenon, or the familiar tuberculin reaction characterized by acute inflammation with necrosis, is regarded as the prototype of the allergic response. Pleural effusion, pneumonia, meningitis and similar outspoken inflammatory lesions are offered as examples of the allergic reaction occurring in the body during the course of progressive tuberculous infection. Krause and certain others disinguish sharply between the qualitative character of the response of the normal and the allergic body. The normal, previously uninfected body is supposed to react to the bacillus by tubercle forma-

tion, never by acute inflammation; the tuberculous (allergic) body is supposed to have acquired the new capacity to oppose the bacillus or its products with ordinary acute inflammation. Thus, Krause writes that when bacilli are introduced into the tissues of the normal body, the development of a nodular tubercle is "the *only* early anatomical response which such tissues will make;" and, further, that this response "is not *essentially* modified by such variables, otherwise decisive, as the numbers and type of mammalian tubercle bacilli concerned." "The essence of the allergic reaction," he continues, "is *exudation*, appearing as typical *inflammation* in solid tissues, and *effusions* in serous spaces. . . . . We never meet with inflammation in tuberculosis except in the allergic animal" (italics Krause's) (2).

When we began this work we, too, held this opinion of allergy—*i.e.*, that following infection the body acquires the ability to react in a manner different qualitatively from that in which it was able to react to tubercle bacilli on first infection. Our observations, however, have made it necessary for us to revise, somewhat, our concept of allergy. That, following infection, the body acquires an altered reactivity or "altered attitude" toward the bacillus is unquestioned; but this altered reactivity is essentially quantitative rather than qualitative. It is not an accurate generalization to say that the reaction to the first contact with the bacillus is always tubercle formation, and that exudative inflammation never occurs except in the allergic animal. Either the normal or the allergic animal can respond to the tubercle bacillus with either tubercle formation or exudative inflammation. Which type of reaction will occur primarily in any instance will depend greatly upon the number of bacilli and where they lodge. If, for example, we introduce a certain quantity of tubercle bacilli, suspended in physiological saline, intratracheally into the lung of a normal animal, there occurs, as we shall see below, an acute tuberculous pneumonia (polymorphonuclear and mononuclear exudate) with slight early necrosis of the exudate. The same suspension of bacilli introduced into the lungs of allergic animals calls forth precisely the same reaction, but in this case the exudate is more plentiful, it reaches its height earlier, and necrosis is more prominent (Figs. 1 and 2). The injection of saline alone leads to no such reaction in either case. On the other hand, if we inject a thin suspension of bacilli into the blood

stream of a normal animal, tubercles develop in the liver sinusoids, accompanied by no appreciable acute inflammatory reaction. The reaction in the liver of the allergic animal after the same injection differs in no way qualitatively from that in the normal; tubercles are formed in the absence of acute inflammation, as can be determined by killing off individuals of a series at different periods of hours following the injection. When not too large doses are used, the only detectable difference between the character of the reaction in the liver of the normal and of the allergic animal is that the tubercles may develop more rapidly in the latter. It is obvious from these facts alone (although numerous other examples could be cited) that (*a*) the normal animal may react to the bacillus with acute inflammation; and (*b*) the allergic animal may react only with tubercle formation.

As for the observation that the normal animal can respond to the tubercle bacillus with acute inflammation, we may point out that, in the same article in which Krause states that the normal animal will respond *only* with tubercle formation, that this response will not be essentially affected by the size of the dose of bacilli, and that acute inflammation in tuberculosis *never* occurs save in the allergic animal, he also writes concerning the reaction of the normal animal that "from the very beginning elements from the blood stream—serum, leucocytes, red blood cells, etc.,—may enter into the structure of nodular tubercle" and that "the extent to which they will appear will depend on such variable factors as "dosage" of localizing bacilli . . . . " (2). This is obviously contradictory to his summarized views which we have quoted above. It is, however, quite in agreement with what we have repeatedly observed, *i.e.*, that with proper dosage in the proper location the normal animal may respond to the bacillus with acute inflammation.

Now although the normal animal can respond to a proper dose of bacilli with acute inflammation (and the recognition of this holds us from the common assumption that every inflammatory response in tuberculosis is necessarily a manifestation of allergy), it is nevertheless true that the tendency of the tuberculous animal to respond with acute inflammation is usually enormously intensified. Furthermore, the tissues of tuberculous animals are peculiarly susceptible to certain products of the bacillus (tuberculoproteins) and are readily killed by them.

In what sense shall we use, then, the term "allergy"? It is best not to define allergy in the loose general terms of "increased sensitiveness," or "altered reactivity" to products of the bacillus, for those terms embrace anaphylaxis, complement fixation, precipitin formation, etc., and it has been well shown that these latter conditions of altered reactivity in tuberculosis can be completely dissociated from the altered tissue reaction which is generally designated by the term "allergy" (Baldwin (11), Zinsser (12)). We shall, therefore, use the word "allergy" here in the following sense, as expressed by one of us in another place:

> The infected body becomes changed in some manner which renders the relatively bland protein of the tubercle bacillus capable of acting upon its tissues as a powerful irritant and poison. As a result of this change, the cells of the allergic body are more extensively damaged and killed by a given amount of tuberculoprotein than are the cells of the normal body; and, furthermore, because of this enhanced irritant action of tuberculoprotein on allergic tissues and because of the resulting more extensive damage and death of cells, there appears a more violent acute inflammation at the site of action of tuberculoprotein in the allergic body. More extensive damage and death of cells, and more extensive acute inflammation constitute, therefore, the local visible expression of the action of allergy. Constitutionally, the greater irritative effect of tuberculoprotein upon the allergic body is manifested by the fact that fever, malaise, prostration and even death will ensue when an amount of tuberculoprotein which is harmless for the normal body finds its way into the blood stream of the allergic one (70).

When therefore, sufficient numbers of tubercle bacilli are introduced into animals rendered allergic by infection with living bacilli, necrosis, accompanied by a severe acute inflammatory reaction, occurs at the site. With very small numbers of bacilli, however, gross inflammation and necrosis are minimal, or may be entirely absent, and a tubercle may be the only visible response to the organisms. This tubercle is quite like that which would develop in a non-allergic animal except that it may reach its full growth somewhat more rapidly, as has been pointed out especially by Rist and Rolland (7), and by Krause and Peters (24), and as we ourselves have frequently observed. This tendency to "accelerated tubercle formation" is undoubtedly a *result* of the allergic state, but we shall have occasion to discuss its actual relation to allergy below. Aside from these histological changes, tubercle bacilli introduced into the body of an infected animal appear

to be held locally—*i.e.*, to spread less rapidly from the site at which they first lodge (13) (42), and furthermore, they are undoubtedly less able to survive than they are in the tissues of a normal animal. It is clear that these two latter effects are manifestations of important immunity phenomena responsible for acquired resistance, and it is largely because of their occurrence along with allergy that the allergic reaction is so widely regarded either as the chief means, or as an exceedingly important one, by which the acquired resistance of the infected body is brought about. Of course, if one includes under the term "allergy" everything, visible and invisible, which happens in the body of an infected animal on reinfection, one is merely, by definition, assuming that resistance and hypersensitiveness are inseparable. But if we restrict the term "allergy" to the acquired hypersensitiveness manifested by the tendency to react locally to the bacillus with exudative inflammation, necrosis, and accelerated tubercle formation, and constitutionally with fever, malaise and prostration, we may say that in spite of the very common identification of allergy with immunity, there is no proof whatever that this hypersensitiveness is responsible or necessary for the delayed spread, or for the more prominent death of the bacilli in the infected, resistant body. It is our purpose here to examine the evidence for and against the current belief that "immunity is achieved through allergy," and to draw attention to certain objections to the assumptions upon which it rests.

Let us examine first the phenomenon of "local fixation" of bacilli in the immune animal. Since the original studies of Koch, innumerable additional experimental observations have suggested that the spread of viable bacilli from a local focus of reinfection may be interfered with in some way in the immune body. The recent experiments of Krause and Willis (42) showed in a striking way that in previously normal animals the lymph nodes draining a cutaneous site of infection were capable of infecting fresh guinea-pigs when excised and inoculated as early as twenty-four hours after the introduction of the bacilli into the skin, whereas regional nodes from similarly treated immune animals were not infective before the end of two weeks after the cutaneous inoculation. This is a truly remarkable difference, and obviously is an expression of a protective (immunity) process of some sort. How can the phenomenon be explained? Is it, as Willis suggests, the result

of a "fixation of bacilli of reinfection by the rapid inflammatory response of the allergic reaction" (13)? Is it actually that the allergic inflammation *mechanically* limits the spread of bacilli from the site of inoculation, as Krause maintains (14)?

In the first place, although it is assumed that inflammation, *per se*, can so perfectly limit mechanically the immediate spread of microorganisms, there is not the slightest proof of this. Certainly, in the case of a well formed abscess, the thick wall of leucocytes must interfere with the drainage of microörganisms from the centre; but were the bacteria primarily prevented from spreading by the inflammation, or was the circumscribing wall formed about them *because* they remained localized in one spot? In support of the latter idea MacCallum states that some organisms "tend to spread diffusely through the tissues. . . . . Such are the streptococci, while the staphylococci are accustomed to concentrate themselves at various points in the tissues, and stir up an intense concentric inflammatory reaction around themselves" (16). This, in effect, places the primary responsibility for the sharp localization of such bacteria upon the growth-characteristics of the microörganism, rather than upon the mechanical effects of the inflammatory exudate; and, indeed, we have frequently seen cases in which the leucocytic response to infection was practically absent, and yet quite sharply limited colonies of bacteria lay in the centres of areas of necrotic tissue. What is it which determines that in some cases a pyogenic peritoneal infection, for example, will remain localized and become walled off, instead of spreading diffusely, although in both cases inflammation is abundant? Is it not primarily dependent upon the fact that, in the first case, the bacteria for some reason remained in one spot until they were encapsulated? Undoubtedly, once walled off their further spread is hindered, but this does not touch the question of why they remain localized long enough to become walled off. Every student of pathology finds himself repeatedly confronted with the fact that certain bacteria at times spread freely through the tissues and into vascular channels in spite of the most intense inflammation, whereas in other cases, in which the infecting "dose" may have been no smaller and the accompanying inflammation even less, the organisms remain sharply localized. In all types of infection the site of the primary lodgment of the bacteria can play,

of course, a fundamental rôle in determining localization or spread; the ability of the body to restrain the growth of the bacteria, and to destroy them, whether through natural or acquired immunity, also enters as a very important factor in determining the rate of spread of lesions, and the relative virulence of the infecting strain is obviously of importance. But the idea that the acute inflammation resulting from the lodgment of the bacteria can in itself mechanically prevent at once the escape of any organisms from the site, especially in the face of the well known increase in lymph flow from areas of acute inflammation, has at present no support in pathological theory or observation. Indeed, it is well recognized that the allergic inflammatory reaction produced about a tuberculous focus by the injection of tuberculin tends to spread the bacilli from the focus; and as for non-specific inflammation, Baldwin, Gardner and Petroff (44) voice common opinion when they write that "as a result of trauma, intercurrent infection or increased functional activity in a part, the small latent tubercle *becomes inflamed and serves as a local source for more or less rapid extension*" (italics ours).

It is possible that in reinfection many kinds of bacteria become fixed at the site of entry in the immune body by some specific precipitin-like mechanism such as that suggested by Opie (43) to explain the local fixation of foreign protein when introduced into the tissues of immunized animals. It is interesting in this connection that Opie, having demonstrated this fixation of foreign protein in the immunized body, regarded the local inflammation of the Arthus phenomenon as a result of the fact that "the foreign substance fixed at the site of injection produces here an intense reaction"—quite the reverse of the view that the intense inflammation mechanically fixes the antigen at the site. Indeed, one can cite experiments reported by Krause and Willis eight years ago as furnishing direct evidence that the mechanical effect of the allergic acute inflammation is *not* the fundamental mechanism which holds the bacilli of reinfection locally. They produced allergic inflammatory reactions with tuberculin in the skin of immunized animals, and into these inflamed area, presumably a stage set for hindering the spread of bacteria, they injected virulent tubercle bacilli, controlling the experiment by injecting the same dose of bacilli into the uninflamed skin of other immunized animals.

Instead of finding, as they had expected, that the injections into the areas of prepared inflammation retarded the spread of the bacilli, they found that those animals developed distinctly more widespread tuberculosis than did the controls in which the injection was made into areas of normal skin. They concluded that immunity is "reduced at the site of an inflammatory tuberculin reaction for at least four days after the application of the tuberculin" and that the "part played by the inflammation of the allergic reaction, considered purely by itself, remains undisclosed" (15). It is difficult to fit that work to their recent conclusion that it is the inflammation which mechanically limits the spread of the bacilli, especially since no further evidence has been obtained in support of that conclusion. It may be said that Baumgarten also found that inoculation of tubercle bacilli into areas of non-specific inflammation furthered, rather than prevented, their spread. At present, therefore, we must say that whatever evidence we now possess is against, rather than in support of the idea that the local fixation of bacilli is a mechanical result of the allergic inflammation.

What the mechanism is which holds the bacilli of reinfection at their site of lodgment, if indeed they actually are so held there, must remain a matter for further study. It is entirely possible that they are not really held fixed at the spot, but that the lack of detectable prompt spread in immune animals may be merely the result of the fact that in such animals the bacilli die in much greater numbers both at the site of inoculation and within any organ to which they are transported. We ourselves have never been able to observe any difference between the numbers of stainable bacilli in the local lesions of normal and of immune animals during the first day or two following measured intracutaneous inoculations, and after this time the number of bacilli in the lesions of the non-immune animals increasingly surpasses that in the lesions of the immunes, until, after the lapse of a week or more, bacilli are exceedingly hard to find in the latter. If bacilli are actually drained so promptly and freely from the lesions in the non-immunes and are held so rigidly *in situ* in the immunes, as the experiments of Krause and Willis indicate, one might reasonably expect to find fewer bacilli in the former. However, the factors of more prominent death of bacilli and loss of their acid fastness in immune animals, and of their freer prolifer-

ation in the non-immunes, introduce complications which render the number of bacilli found in such lesions an insufficient index of the number drained from them.

This much we can say: the study of lymph nodes draining the sites of allergic inflammatory lesions in the human being with acquired resistance always reveals the sinuses of the nodes full of cells and debris drained from the lesions. At least, the lymphatic drainage from the inflammatory site is perfectly free. Bacilli are, however, usually very hard to find in such nodes. It seems clear, therefore, that if the bacilli are actually held fixed, locally, in the lesion drained by the nodes, it must be by means of some *specific* (precipitin-like?) mechanism which does not interfere with the free movement of other particulate matter, and not merely by the mechanical outpouring of inflammatory exudate. And until we have more precise information on the question it must be remembered that the inoculation results in the experiments of Krause and Willis might be interpreted on the basis of the well established fact that there occurs a much greater destruction of bacilli in immune animals than in normal ones. The experiments cannot be regarded as having "established beyond doubt that after their entrance into the body of immune guinea-pigs there occurs a marked delay in the time of first appearance of tubercle bacilli in the various tissues in which they are accustomed to localize" (10). They showed only that after a given lapse of time following reinfection there were fewer *viable* bacilli in the various organs of the immune animals. There is, furthermore, a source of error in the experiments which makes interpretation of the results difficult. This consists in the fact that the lymphatics of the skin are readily injected mechanically when fluid is introduced under pressure. Willis, himself, confirmed this fact during his work by injecting Prussian blue in the same amount and under the same conditions which he had employed in the tubercle bacillus injections. On clearing the areas by the Spalteholtz method he found that "in about half of the animals lymphatic injection of greater or less degree occurred" (13). The direct introduction of bacilli into the lymph stream in experiments which are supposed to demonstrate local immobilization of those bacteria by inflammation, is a serious complication.

Now as regards the relation of the allergic reaction to the increased ability of the immune body to restrain the proliferation and to bring

about the death of the tubercle bacillus, although there cannot be the slightest doubt of the existence of this increased power, in spite of years of investigation the change which renders the immunized body unfavorable to the tubercle bacillus remains still completely obscure. Such an effect could result from the presence of lysins or other bactericidal or growth-restraining properties in the plasma of the immune animal; or the phagocytic cells may have developed an increased ability to digest the bacillus; or, in some more subtle and obscure way, implying no active process of destruction, the fluids and cells of the immune body may have become so altered that the bacillus finds there a poorer medium in which to survive.

No one has yet been able to demonstrate satisfactorily that lysins or specific bactericidal properties are present in the plasma of the immune animal, or in the inflammatory fluids at the site of an allergic reaction; nor has a greater digestive power of the phagocytes been proven. Rich and Lewis have recently made an especial study of the latter possibility, comparing *in vitro*, by the method of tissue culture, the digestive powers of polymorphonuclear and mononuclear phagocytes from normal and from immunized animals. The results of many such experiments have, up to the present writing, been only equivocal. Since the progress of tuberculous infection is not retarded by implanting the bacilli in fresh areas of acute inflammation, the mere rapid mobilization of phagocytes at the site of the allergic reaction cannot be regarded as the mechanism responsible for the increased destruction of the bacilli. Indeed, our attention was first drawn to the possible dissociation of allergy and resistance when we observed that, whereas single or several bacilli lodging at any one point are not sufficient to elicit an allergic inflammatory reaction of visible degree, yet animals with acquired immunity are definitely resistant to virulent bacilli even when the latter are introduced in thin suspension intravenously in such a manner that only one or two lodge at any one site. Under proper conditions of dosage the difference in the rapidity with which tubercles will be formed in the tissues of the normal and the immune animals will be truly negligible; and yet, after the lapse of a few weeks, the difference between the amount of tuberculosis in the normals and in the immunes is tremendous.

Although it is at present widely believed that the allergic reaction is

an essential mechanism of immunity, there is no proof of any sort that this reaction is necessary for the more rapid death of bacilli in the immune body. As we have said, the essence of the matter of acquired resistance is that the bacilli cannot thrive as well in the previously infected body as in the normal one; and although we are at present unable to speak with certainty of the meaning of allergy in relation to immunity, it is our belief, for numerous reasons, that the bodily change responsible for this acquired interference with the life of the bacillus is, in whatever it consists, quite separate and distinct from the forces which are concerned in the allergic inflammatory-necrotizing tendency. We believe that it is a mechanism which develops after infection, usually coincidently with, but separately from, the allergic sensitization, even as it is well known that, in tuberculosis, anaphylactic sensitization to the bacillary proteins develops entirely independently of immunity (18). Indeed, in favor of the idea that "immunity is achieved through allergy" we have, really, only the fact that, in the experimental animal, both immunity and allergy appear at about the same time after infection, and that they are usually co-existent thereafter. *It is, however, by no means established that they are invariably co-existent.*

Against the view that the allergic inflammation is responsible for resistance we may recall again the experiments of Krause and Willis, in which tubercle bacilli were implanted into areas of allergic inflammation produced by tuberculin. The resulting infection was so extensive in comparison with that in controls that, as we have said above, the investigators concluded that immunity is "reduced at the site of an inflammatory tuberculin reaction for at least four days" (15). It is, as we have pointed out, difficult to harmonize this with Krause's belief that the allergic inflammation mechanically retards the spread of the bacilli; and it is still less easy to reconcile it with his more recent statement that "acute inflammation, nonspecifically and of itself, can exert profound biochemical and biophysical effects on tubercle bacilli" which lead to their death and disintegration (17).

Against the view that resistance is determined by allergy we may, further, refer to the attempts to produce acquired resistance by the injection of dead tubercle bacilli. Since the time of Koch, investi-

gators have striven to induce resistance by this means; but, in contrast to the powerful resistance conferred by infection with living bacilli even of very low virulence, the results with killed bacilli were, on the whole, so unimpressive that they justified the general opinion expressed a few years ago by Krause that "increased resistance can be obtained only by making the animal tuberculous; that is, by inoculating the animal with *living tubercle bacilli*" (4). Recent work by Zinsser and, more especially, by Petroff and Stewart (33), has shown that this opinion is not strictly correct. A certain degree of protection can, apparently, be conferred by inoculation with killed bacilli. It is, however, not so striking a degree of immunity as that produced by infection with living bacilli. Petroff and Stewart write concerning the somewhat longer period of survival, following virulent inoculation, of animals treated with dead bacilli as compared with untreated controls: "This is not a remarkable result, but it clearly establishes a relative resistance due to the injection of dead bacilli" (33). The tuberculous lesions in the animals treated with dead bacilli were also less extensive than those in untreated controls, after virulent inoculation of both. After inoculation with rather large doses of virulent bacilli, the length of survival of the animals treated with dead bacilli was considerably less than that which would have been expected in animals immunized with living bacilli. We do not intend to bring into question the possible value of the prophylactic use of dead bacilli. Perhaps they may confer an immunity sufficient to restrain effectively the small numbers of bacilli responsible for childhood infections. Certainly the investigations of Petroff and his co-workers are very suggestive in this respect. We are merely pointing out here that the degree of resistance to a rather large dose of virulent bacilli was less than that to be expected from immunization with living bacilli.

What now of allergy produced by dead bacilli? If allergy be the mechanism of resistance, allergy should be less highly developed in animals treated with dead bacilli, in comparison with the hypersensitiveness of animals which are more highly resistant because of infection with living bacilli. On the contrary, however, inoculation with dead bacilli produces a degree of hypersensitiveness as great as that evoked by inoculation with living bacilli; and it is a durable hypersensitiveness. In regard to this point Petroff and Stewart state,

after a thorough study of the point, that "the local cutaneous allergic reaction in animals sensitized with dead bacilli varies in no way from that in infected animals" (19).

We are, then, confronted with the circumstance that although an animal inoculated with dead bacilli develops just as marked an allergic hypersensitiveness and exhibits just as marked allergic inflammatory reactions as does an animal inoculated with living bacilli, the ability of the former to cause the death of the bacillus and to hold its growth in check (immunity) is distinctly less than that of the latter. To us this appears to indicate that the death and the restriction of growth of the bacillus are effected by some mechanism separate from that of the allergic inflammation—by an independent mechanism, which does not always parallel in intensity the development of allergic hypersensitiveness.

The above facts indicate that an identical and high degree of allergy may exist in different individuals which exhibit very different degrees of acquired resistance. Is there, now, any evidence that a high degree of acquired resistance may be present by the side of a low degree of allergy? We may mention in this connection the statement of Calmette that allergy may disappear some time after a protective inoculation with his BCG bacillus of low virulence, but that acquired immunity nevertheless persists (45). And we may cite, further, the recent experiments of Willis, in which he found that after a lapse of two and a half years following an immunizing inoculation with R_1 bacillus of low virulence, guinea-pigs had practically lost their allergy, but on reinfection with a virulent bacillus they showed as pronounced a degree of immunity as did animals which were highly allergic. Willis justly remarks that, if immunity is really a function of allergy as he believes it to be, "one would expect, in animals with healing or healed tubercle and with allergy low or hardly detectable, to find a much reduced immunity, if, indeed, it were to be discerned at all;" however, "notwithstanding this greatly reduced and practically absent allergy, such guinea-pigs, at thirty months after infection, were found to possess a high specific immunity to reinfection with virulent tubercle bacilli" (46). In an attempt to account for this unexpected disproportion between the degree of allergy and of immunity exhibited by these animals, Willis (46) points out that although allergy had become feeble or

indetectable, it reappeared again, in three out of four animals, in a shorter time after reinfection than hypersensitiveness ordinarily develops following a first infection.[4] At the best, however, the experiments show that the bacilli of reinfection must have remained in the body unmolested by any possible action of allergy for at least four days following their introduction, for the return of allergy could not be detected before that lapse of time; indeed, in one of the four animals no allergy could be detected even at four days after reinfection, and yet this animal showed just as great a degree of resistance as the rest—a resistance as marked as that observed in animals in which the bacilli are met at once by a vigorous allergic reaction. In the face of this it is difficult to believe that a prompt allergic reaction is necessary for destroying or for preventing the spread of the bacilli in the immune body—especially since Krause has shown that within four days after the introduction of bacilli into the subcutaneous tissue of non-allergic animals the bacilli have spread throughout the entire body and can be recovered from the viscera.

It is pertinent to the matter under discussion to recall that Krause and others offer, in support of the view that resistance depends upon allergy, the fact that allergy is said to wane during pregnancy and the puerperium—conditions during which resistance to tuberculosis is well known to become depressed. The actual state of allergy in pregnancy and the puerperium needs further investigation, for very little has been done, and that little is somewhat contradictory; but even if it be true that allergy is depressed in these states, it is difficult to offer this as an explanation of the lowered resistance, and at the same time to explain the high resistance of animals in which allergy has become depressed by stressing the fact that further infection rapidly restores a depressed allergy. That women, dying rapidly from an outbreak of tuberculosis during pregnancy or the puerperium, do usually possess a high degree of allergy is clear to us from the presence of marked allergic inflamma-

[4] It is conceivable that the more prompt development of allergy observed following the reinfection of animals which have lost their hypersensitiveness, may be the result of the fact that, being immune, there occurs a more rapid destruction of bacilli introduced into their tissues than takes place in the normal body, and therefore a more prompt exposure to the sensitizing protein liberated from disintegrated bacilli.

tory-necrotic lesions in such cases in our autopsy material; and Aschoff, likewise, writes in this connection that "bestimmte physiologische Umstimmungen, wie das Puerperium, lassen die exudative-defensiven Formen stärker hervortreten" (3). And yet in the face of these stronger allergic reactions, resistance is unquestionably greatly diminished. As a further example of the inconsistencies which are so frequently encountered in the literature favoring the identity of allergy and immunity, we may offer the following from the paper of Nobecourt and Paraf (22),—one of the very few studies dealing with the state of allergy during pregnancy, and a widely quoted paper:

> Souvent donc, à la fin de la grossesse at après l'accouchement, les tuberculoses pulmonaires en activité subissent une aggravation et prennent une marche aigue, les tuberculoses latentes peuvent être reveillées et *se manifester notamment sous forme de pleurésies, de congestions pleuro-pulmonaires, de spléno-pneumonie.* Ce coup de fouet donné à la tuberculose semble lié à un fléchissement de l'immunité sous l'influence de la puerpéralité, *comme en témoigne à ce moment l'attenuation et même la disparition de la cuti-réaction à la tuberculine.* (Italics ours.)

In the same breath in which these investigators stress the special tendency to the development of lesions which we must recognize as unmistakably and vigorously allergic in character (acute pleurisy and pneumonia), they state that while these lesions are being formed, allergy is depressed or completely absent.

It is of importance to discuss, in connection with the question of the relation of allergy to immunity, the fact that by administering repeated, increasing doses of tuberculin to the allergic human being, a tolerance or, more properly, a desensitization to tuberculin may be established to such a degree that the individual becomes able to tolerate relatively enormous doses without inflammation, necrosis or constitutional symptoms. Treatment in this manner with tuberculin has been widely practised for years, and has been found to be beneficial in certain forms of tuberculosis even by those who regard allergy as the means of resistance. It is difficult for us to understand the beneficial action of abolishing allergic hypersensitiveness if it means abolishing the mechanism of resistance, for not even the most extravagant enthusiasts could believe that tuberculin treatment rids the body of bacilli; and it is not possible to believe that the loss of sensitiveness is merely a result of encapsulation of the lesion, for allergy is commonly high

when the only lesion in the body is the minute, thoroughly encapsulated protective one, and it frequently sinks almost to zero in the presence of severe advancing lesions. If, however, resistance is independent of allergy, the reduction of the necrotizing effect of hypersensitiveness to the bacillary proteins could easily be understood to be beneficial. When we realize that tissue necrosis in tuberculosis is almost entirely the result of allergic hypersensitiveness to tuberculoprotein, it becomes clear that the correct interpretation of the significance of allergy in relation to immunity may be a matter of considerable practical importance. If allergy is not necessary for resistance, obviously one of the best things that we could do would be to desensitize the body and so free the tissues from the danger of being destroyed by traces of bacillary products.

Since it is generally believed that the allergic inflammation is an immunity reaction concerned with killing or restraining the growth of the tubercle bacilli, the usual explanation of the beneficial effects of the tuberculin treatment is that the introduction of tuberculin into the body causes inflammatory reactions about the tuberculous foci, and that these reactions in some way help to destroy the bacilli contained in the lesions and also "stimulate fibrosis." Now it is true, without question, that a sufficient subcutaneous dose of tuberculin will produce an inflammatory reaction, and even necrosis, about existing tuberculous foci elsewhere in the body. It was long ago realized that large doses of tuberculin can be very dangerous to the infected body because the necrosis and inflammation which large doses cause about tuberculous foci result in extension of tissue damage and in spread of bacilli. In using tuberculin therapeutically, therefore, it has long been the practice to be careful not to administer doses large enough to produce severe perifocal reactions. Instead, very small doses are injected at intervals of every few days. But repeated small injections usually produce a complete "tolerance" to the dose injected, so that a larger dose has to be administered in order to produce any reaction at all. The practice is, therefore, to increase the size of the dose gradually. With this procedure, a point may be reached at which as much as several cubic centimetres of full strength tuberculin can be injected without evoking a reaction in a body which, at the start, may have reacted strongly to the injection of 0.1 cc. of a 1:10,000 dilution of

tuberculin. This procedure is often spoken of as mithridatism, or the production of "tuberculin tolerance." It is, however, more properly to be regarded as a desensitization to tuberculin—*i.e.*, as the abolition of the infected body's acquired, abnormal hypersensitiveness to tuberculoprotein.

We have said that it is the generally accepted view that the beneficial effect of tuberculin therapy results from the mild inflammation which the injections may produce about the tuberculous foci. However, it is well recognized that the beneficial effect may be definite even when the perifocal inflammation is so slight that it has to be assumed to be present. Thus, in tuberculosis of the skin great benefit may follow treatment even when doses are so regulated that not the slightest visible reaction occurs about the lesion (47), and the same is true of ocular tuberculosis (48). It is exceedingly difficult to believe that an inflammatory reaction of such insignificance that not even hyperaemia can be detected by careful scrutiny, can retard the progress of a tuberculous infection. It is our belief that any beneficial effect which may follow treatment with tuberculin is less referable to perifocal inflammation than to desensitization, and will occur only in those cases in which desensitization of a proper degree has been accomplished. We have already pointed out that there exists no proof that the allergic inflammation can, in itself, bring about the death of the bacilli. As for the "stimulation of fibrosis" by perifocal allergic reactions, no such stimulation is necessary. The encapsulation or scarring of a tuberculous focus by connective tissue is merely a process of non-specific repair; it is the same process which inevitably follows death of tissue, no matter how produced, unless regeneration of the destroyed tissue occurs. It is not a part of the process of inflammation (MacCallum (49)). It is in no sense a necessary result of even a violent inflammation. The complete resolution, without fibrosis, of the extensive inflammation of lobar pneumonia may serve to illustrate the truth of these statements and to warn one against the assumption that "the end result (or shall we say the purpose?) of every inflammation pursuing a normal, uninterrupted and complete course is fibrosis" (23). Furthermore, that acute inflammation is by no means *necessary* for efficient connective-tissue repair is familiar to anyone who has observed the organization of thrombi. The extraordinary vascularity characteristic of newly form-

ing connective tissue, and resulting from the rapid new formation of wide capillaries, obviates the need of an inflammatory capillary dilatation to bring blood to the part. Connective-tissue repair will proceed, with surety and success, to scarring or encapsulation of any area of tissue which has been destroyed by the tubercle bacillus or by any other microörganism, if there is no marked circulatory obstruction about the area, and if the connective tissue is not destroyed as fast as it is formed by the effects of the infecting organism. In the case of the tubercle bacillus, we are dealing with an organism which, as is well known, has a little power to cause necrosis in the unsensitized body; but, when allergic hypersensitiveness has been acquired, the products of the bacillus, in minute concentration, can destroy tissue readily. Any attempt at the formation of connective tissue about a focus of bacilli in the allergic body can be thwarted by the lethal effects of the tuberculoprotein liberated from those bacilli. This interference with repair is, unfortunately, furthered by the well known circumstance that the cells immediately adjacent to a focus of bacilli acquire a much higher degree of sensitiveness to tuberculoprotein than do those at a greater distance. It must be clear therefore that the formation of connective tissue about a tuberculous focus always proceeds under unfavorable local conditions in the allergic body. The success or failure of adequate fibrosis will always depend largely upon the balance between the degree of hypersensitiveness and the amount of tuberculoprotein liberated from the bacilli in the lesion. In autopsy material there is always ample evidence of attempted connective tissue repair about any chronic progressive tuberculous lesion, but the newly forming granulation tissue can often be seen to become necrotic as rapidly as it is formed.

If, now, we decrease the fatal hypersensitiveness of the cells to tuberculoprotein by means of repeated, desensitizing doses of tuberculin, and at length reach a point at which the tissues approximate their normal indifference to the products of the bacillus, is it not reasonable to expect that the formation of connective tissue and the encapsulation of the bacilli can proceed with greater success? If acquired resistance—the unknown mechanism which restrains the growth of the bacilli in the infected body—is actually, as we believe it to be, a thing separate from allergic hypersensitiveness, and can be left intact after desensitization by tuberculin therapy, one may expect that its effects

will be aided by the greater security against necrosis which desensitization assures any connective tissue formed about a lesion.

A study of the literature concerned with tuberculin therapy leads us to believe that the conflicting opinions as to its value may arise from the fact that it has not always been given a fair trial from the standpoint of deliberate efforts directed toward thorough desensitization. The "perifocal inflammation" concept has dominated its use, leading frequently to the cessation of treatment when hypersensitiveness declined; and most often no direct attempt has been made to restore the patient to his natural condition of complete tolerance toward tuberculoprotein. This probably cannot be accomplished in every instance; and there will, besides, always be cases in which the infection is too heavy, in which acquired resistance is poorly developed, or in which the disease has progressed too far to be appreciably checked by desensitization; but we believe that treatment with tuberculin may, in general, be of value in proportion to the degree to which one proceeds from the standpoint that hypersensitiveness to the bacillary products is the chief cause of tissue destruction and that this hypersensitivity is not essential for resistance. We have, ourselves, as yet no experimental proof of the beneficial effect of complete desensitization, but one of us is engaged at present in such experiments. We may, however, quote here the clinical experience of such careful students of tuberculosis as Hamman and Wolman, as stated in their book on "Tuberculin in Diagnosis and Treatment":

> In the majority of cases such a change for the better is associated with the development of a tolerance for tuberculin. This is a clinical fact, whatever our theories may be. . . . . We must not blind ourselves to the well attested clinical observation that the average tuberculin patient shows, simultaneously with his improvement under tuberculin, a tolerance for tuberculin by whatever route. This remains a fact generally true, in spite of the citations of individual cases showing departures from this rule (*e.g.*, Neumann's) and in spite of oscillations of theories of immunity (20).

This statement is especially valuable to the present argument because it is made by observers who, themselves, accept the idea that the beneficial effects of tuberculin therapy are referable to the "mild reactions" which "promote fibrosis" (21).

To return to our question whether a high degree of resistance can

exist with a low degree, or an absence, of allergy, we believe that the more satisfactory physical condition and the more active restraint of the progress of lesions in patients who have had their hypersensitiveness reduced through desensitization is important affirmative evidence.

In support of the belief that acquired resistance is a thing separate from allergic hypersensitiveness we have pointed out that there is no real evidence that the allergic inflammation is responsible for local fixation or for the more efficient destruction and inhibition of growth of bacilli in the immune body; and, further, we have presented evidence that allergy and acquired resistance do not necessarily parallel each other—that resistance, for example, may be maintained in a high degree in the virtual absence of allergy. In any consideration of the relation of allergy to resistance one must keep clearly in mind that, whatever may be our interpretation of the purpose of hypersensitiveness, the allergic reaction is an evidence not of greater resistance of the individual tissue cells to the products of the bacillus, but of greater susceptibility. The allergic body is enormously more susceptible to the local and general effects of tuberculin than is the normal body. Locally, death of tissue is readily produced by amounts of bacilli, or of bacillary products, which do not harm the non-allergic body at all. Intravenously, an amount which will be completely innocuous to a normal animal will kill an infected, allergic one. We are thus confronted with what appears at first sight to be a paradox: the infected body is more susceptible at the same time that it is more resistant than the normal one. There is actually, however, no contradiction in this; the infected body prevents the growth of the bacilli and causes their death more readily than does the normal body—*i.e.*, it is resistant to *living bacilli;* at the same time, this resistant body becomes sensitized to the *bacterial products* resulting from the death and disintegration of the bacilli, just as the body becomes sensitized to any foreign protein introduced into the tissues—*i.e.*, it is hypersusceptible to tuberculoprotein.

The allergic hypersensitive reaction is not specifically an attack upon living bacilli. It follows, in extreme degree, the injection of a simple water extract of the powdered bacillus. It is important to remember that a similar inflammation and necrosis can be produced by the local injection of any non-bacterial, bland protein, such as egg albumen,

to which the body has been sensitized. It is generally believed that in the case of the tubercle bacillus it is not the intact, living bacilli which initiate bacterial allergy, but, rather, the products resulting from bacillary disintegration. Even Zinsser, who holds the belief that allergy is of fundamental importance in acquired resistance in tuberculosis writes: "Bacterial allergy is a condition in which the body is sensitized to a bacterial antigen. We believe that this antigen, in its most potent form, results from biological disintegration of the bacteria. . . . . The allergic state represents an increased capacity on the part of the tissues to react to this antigen" (5). We agree completely with this much of Zinsser's viewpoint. The allergic state in tuberculosis represents an increased capacity on the part of the tissues to react, not against living bacilli, *but to a bacterial antigen which is liberated as a result of the disintegration of the bacilli.* We believe, in other words, that the mechanism leading to the death of the bacilli is in operation *before* the allergic reaction begins—that the sequence of events following the lodging of bacilli anywhere in the infected body is: first, the action of resistance leading to death of bacilli, and only then, second, the allergic response of the tissues which have become sensitized to the products of disintegration of the bacilli.

Even though the mechanism of resistance be separate from allergy, we must enquire whether or not the allergic reaction can be of assistance in any way to the former mechanism, for the thought of "accelerated tubercle formation," and of the many infections in which acute inflammation serves as a means of bacterial destruction, always tends to make one feel that the setting of the inflammatory mechanism on a "hair-trigger" by means of allergy must aid in the destruction of the tubercle bacillus.[8]

First, as regards the more rapid formation of tubercles in the allergic body, while it is clear that this process tends to aid mechanically in the

[8] We shall not dwell here upon the alleged beneficial effect of allergic necrosis, for although caseation followed by cavity formation in the lung, or by ulcer formation on mucous surfaces, does rid the body of great numbers of bacilli, this is an accidental result of the location, and not an orderly protective mechanism. Such ulceration of lung or intestine is often more dangerous than beneficial, for it directly spreads the infection; and the 'ulceration' of a caseous tubercle of the brain into the subarachnoid space leads only to meningitis.

prevention of the spread of the particular bacilli enclosed in each tubercle, it is, nevertheless, neither a fundamental nor a decisive factor in acquired resistance. The mere spread of bacilli over the body is not, in itself, the dangerous thing. Those bacilli must be able to proliferate freely where they lodge, and we know well that the mere formation of a tubercle about bacilli in the non-immune body does not necessarily prevent their multiplication. We have, many times, deliberately spread bacilli all over the body of animals with acquired resistance by injecting a thin suspension directly into the blood stream; yet those resistant animals show very few lesions after a lapse of weeks, and resolution and disappearance of tubercles during this period can be followed with ease. On the other hand, normal controls receiving the same dose at the same time die of progressive tuberculosis and at autopsy show masses of tubercles throughout the viscera. These tubercles, containing many living bacilli, had grown progressively larger during the period, instead of regressing as in the case of the immune animals. Indeed, the regression of the lesions in the immunes was only a result of the death of the bacilli contained in them. When very fine suspensions of bacilli are used in such experiments, the difference in quality or rapidity of tubercle formation in the immunes and controls may be negligible in animals killed every twenty-four hours after the injections. It is, therefore, clear that some factor other than mere tubercle formation was in operation in the immune animals in restricting the growth of the bacilli. We shall point out later that every human case with progressing tuberculosis reproduces this animal experiment, in that the spreading of bacilli all over the body during periods of bacillemia leads usually to no progressive visceral metastatic lesions because the body is resistant. These facts show plainly enough that the action of accelerated tubercle formation in preventing the spread of bacilli need not be stressed as a very important aid to immunity. Nor must we forget that any mechanical restraint of the bacilli by the allergic accelerated tubercle formation is all too commonly completely neutralized by the necrotizing effect of allergic hypersensitivity leading to necrosis of the tubercle and escape of the bacilli into the blood stream, as we shall see.

Now as regards the allergic acute inflammation: that this is a beneficial thing to the hypersensitive body we do not question. Since

the products of the tubercle bacillus are exceedingly poisonous to the allergic body it is clear that the prompt outpouring of an inflammatory exudate wherever those products come in contact with the tissues can serve to dilute and to restrict the action of the injurious agent just as is the case when sulphuric acid or any other poison attacks the tissues. In other words, the allergic reaction is a response to, and undoubtedly helps to neutralize, the injurious effects of the products of bacterial disintegration in the hypersensitive body. In this sense the inflammation is protective. As to the effect of the allergic inflammation upon the living bacillus, that is an entirely separate problem. If it could be shown that the phagocytic cells or the fluids of the body with acquired resistance possess greater bactericidal powers than do those of the normal body, it would be clear that it could be advantageous to have them brought more rapidly to the site of lodgment of tubercle bacilli, and in this sense the allergic inflammation could assist the *separate, bactericidal* mechanism of immunity. We have said that up to the present the many attempts to demonstrate the existence of such properties in the cells or fluids of resistant animals have been without success. Unless such acquired bactericidal properties do exist in the materials of the inflammatory exudate of the resistant body, the mere presence of inflammation at the site of lodgment of bacilli will be of no more value in restraining the growth of the bacilli than it is in the normal animal, and non-specific, acute inflammation does not retard the development of tuberculosis in the non-immune animal. If, on the other hand, the mechanism of acquired resistance is not a specific bactericidal mechanism, but rather some more subtle incompatibility of bacillus and host which interferes with free parasitism, there is no reason to believe that the inflammation of allergy would in any way serve that incompatibility. That a tendency to exudative inflammation is completely unnecessary for the successful operation of an immunity of this latter type must be obvious from the fact that the reaction of the normal rabbit to virulent human bacilli is as slow and leisurely and as proliferative in character as is that animal's reaction to virulent bovine bacilli; and yet the latter infection progresses to a fatal termination while the former is completely resisted and does not. The same is true of the reaction of the guinea-pig to the R_1 human bacillus of low virulence as compared with its reaction to a

virulent strain. There is not the slightest evidence that the phagocytes or fluids of the rabbit are able specifically to destroy the human more easily than the bovine bacillus, or that the guinea-pig has a more efficient specific bactericidal defense against a strain of low virulence than against one of high virulence. The most that we can say is that the growth requirements of different types and strains of tubercle bacilli must be different, and that natural immunity may often depend entirely upon whether a given animal body is or is not able to satisfy those requirements. In the case of acquired resistance to the tubercle bacillus, we feel that the evidence at hand at present makes it not unlikely that there has occurred in the resistant body some change which places it in a condition comparable to that present in natural immunity—a condition which merely renders the body a less favorable medium for parasitism by the tubercle bacillus. It is obviously of great importance to continue the attempt to determine what it is which inhibits parasitism in natural as well as in acquired immunity in all infections in which specific bactericidal properties of phagocytes or body fluids cannot be demonstrated.

We have pursued this rather lengthy discussion of the relation of allergy to resistance for the reason that this is one of the most important matters involved in the pathogenesis of tuberculosis. Every observant student of the disease knows well that constitutional symptoms and extensive necrosis of tissue are directly dependent upon allergic hypersensitiveness. It is, therefore, of fundamental importance, not only for theoretical but also, perhaps, for practical reasons, to know whether or not this hypersensitiveness which, in effect, converts the bland protein of the bacillus into a most violent poison, is necessary in any way for the operation of acquired immunity.

Since we have learned to realize that the specific, inherited, coördinated reactions of the body usually serve the purposes of protection and survival, it is quite natural to feel that the complicated mechanism of allergy, too, must exist for some serviceable end; and we would be the last to foster the view that protein hypersensitiveness is a purely harmful state, developed accidentally, and leading only to tissue destruction, constitutional symptoms and death. But it is one thing to believe that the reaction exists for some useful purpose, and quite another thing to believe that it protects the body against the tubercle

bacillus. It is our belief that the various forms of protein hypersensitiveness (anaphylaxis, tuberculin allergy, Arthus phenomenon) are in all probability merely different manifestations of one fundamental reaction brought into play under different conditions. What the basic intent of that fundamental reaction may be (digestion of foreign protein, maintenance of the specificity of the species proteins?) we do not know; but the disastrous effects of the repeated introduction of foreign protein into the blood stream (anaphylaxis) or directly into the tisssues (allergy, Arthus phenomenon) may very well be accidental results of a highly organized, benign, serviceable mechanism which, under these circumstances has been forced into action in situations and under conditions quite different from those which surround its intended activity. The *parenteral* introduction of large amounts of foreign protein is highly abnormal, whether we force it into the tissues with a syringe or whether it is deposited there as a result of the disintegration of bacteria which have forced their own way, parenterally, past the normal barriers. From such a point of view, a hypersensitive reaction initiated by the liberation of a bacterial protein from disintegrating bacilli has, basically, the same meaning and purpose as a hypersensitive reaction resulting from the injection of egg-white into sensitized tissues. It is no more difficult for us to regard the allergic tissue damage in bacterial infections as an unfortunate accident, resulting from the parenteral liberation of foreign protein by the bacillus, than it is to regard anaphylaxis to tuberculoprotein as of no special use as an aid to immunity. Certainly an animal may be highly anaphylactic to tuberculoprotein and yet possess not the slightest degree of acquired immunity; or it may be highly immune to the bacillus, after infection, and yet not at all anaphylactic to tuberculoprotein.

We wish to reiterate that, in drawing into question the value of allergy in acquired resistance, we are in no sense questioning the value and good service of the inflammation which attends the allergic reaction. As we have said, however, this inflammation appears to us to be directed primarily toward the neutralization of the noxious effects which tuberculoprotein exerts upon the hypersensitive body, rather than to be a bactericidal attack against the intact, living bacillus.

We are, ourselves, keenly aware of the great attractiveness of the idea that bacterial allergy operates to destroy the invading micro-

organism. However, the enthusiastic eagerness with which this idea is so generally seized upon may profitably be tempered by a critical examination of the evidence upon which it rests. In the above discussion we have sought to analyze that evidence, and to emphasize that, in the present state of our information, it is wiser not to interchange too glibly the terms "allergy" and "resistance." Nor shall we profit by the use of evasive phrases such as "allergy is an index of resistance," etc. The question to be met squarely is this: Is, or is not, tissue hypersusceptibility to tuberculoprotein necessary for the more efficient destruction and restraint of growth of the bacillus observed in the body with acquired resistance? We have given reasons for the belief that it may not be necessary; but further experimentation directed toward the solution of the problem is urgently required.

Since the proper interpretation of the meaning of allergy and its relation to resistance demands an understanding of the bodily changes responsible for this acquired hypersensitiveness, it is necessary to enquire:

VII. WHAT IS THE UNDERLYING MECHANISM OF ALLERGY?

Any explanation of the mechanism of allergy must at least account for the three observed reaction-tendencies of the allergic body exposed to the bacillus—damage and death of cells, inflammation, and accelerated tubercle formation. Since a given amount of tuberculoprotein produces far greater inflammation and necrosis in the allergic body than in the normal one, it is clear that the allergic body has become changed in such a way that either tuberculoprotein itself can now act directly upon it as a powerful irritant and noxa, or else that the body has acquired the power to act upon tuberculoprotein with the resulting formation of a noxious substance which then damages the cells. Both the inflammation and the necrosis of allergy are merely the manifestations of the action of an irritant to which the allergic body is susceptible. What is the explanation of this fact that tuberculoprotein is a violently irritating poison to the tissues of the allergic body?

In the light of what is known of protein hypersensitive reactions, it is generally believed that the most probable explanation of allergic inflammation and necrosis in tuberculosis is that it is the result of an antibody-antigen reaction in which the bacillary protein constitutes

the antigen which reacts with an antibody formed during infection. According to this view the cells of the sensitized body might be perfectly normal, and the plasma and tissue fluids contain an antibody capable of acting upon the bacillary antigen to yield an irritating substance toxic for the normal cells. If this were so, the addition of tuberculoprotein to the plasma of an allergic animal should result in the formation of this toxic substance which would cause inflammation and necrosis in animals whether allergic or normal. We have carried out experiments of this nature repeatedly, but we have never been able to produce anything comparable to the allergic reaction by the intracutaneous injection of mixtures of tuberculin and allergic plasma which had been previously incubated for varying periods of time. Fluid from the site of allergic inflammatory reactions has also failed to produce reactions in normal skin. Zinsser has recently reported similar negative results (50).

A second possiblity to be considered is that the active antibody does not circulate freely in the body fluids, but is bound to the tissue cells in such a way that the antigen-antibody reaction leading to the formation of the injurious substance takes place actually within or upon the cells. Zinsser feels that he has obtained some evidence that this is the case by injecting mixtures of tuberculin and extracts of ground up tuberculous tissue into the skin of normal animals, but he speaks of his positive results as "irregular and occasional" (50).

Finally, it is conceivable that the production of cellular damage through allergic hypersensitivity is a result of an antibody-antigen reaction dependent upon antibodies present both in the tissue cells and in the body fluids.

For numerous reasons, into which we shall not enter here, we felt that experiments of the nature mentioned above left much to be desired in the matter of proving or disproving the existence of a circulating antibody capable of reacting with tuberculoprotein; and, since it had never been proved whether or not the individual cells of the allergic body are inherently changed in any manner which renders them more sensitive than normal cells to the products of the tubercle bacillus, Rich and Lewis (8) applied the method of tissue culture to the study of the problem. Thoroughly washed fixed tissue and blood cells of allergic and of normal guinea-pigs were placed for culture in the

plasma of allergic and of normal animals, and the same amount of tuberculin was added to all of the cultures. In this manner, normal and allergic cells were exposed to tuberculin while surrounded by normal and by allergic plasma. The results of hundreds of such cultures showed clearly that the cells from allergic animals were regularly and promptly killed when exposed to tuberculin, regardless of the plasma in which they were placed; while the cells from normal animals, regardless of the plasma in which they were placed, remained alive and multiplied when exposed to the same concentration of tuberculin which rapidly killed the allergic cells. Both the normal and the allergic cells were unaffected by exposure to the glycerine-broth control fluid. It is clear from these experiments that no plasma antibody is necessary for the damage and death of allergic cells exposed to tuberculin; the individual cells of the various tissues of the allergic body are themselves actually hypersensitive to tuberculoprotein. Allergy, therefore, resides in the cells. Whether the cellular injury and death is a result of the interaction of an intracellular antibody with the bacillary antigen, or whether some other principle lies at the bottom of this cellular hypersensitiveness, we are at present unable to say. It is, however, probable that the local allergic reaction in tuberculosis is of the same general type of reaction that follows the local injection of foreign protein, such as egg albumen, to which the body has been sensitized—the so-called "Arthus phenomenon." However, up to the present no one, including ourselves, has been able to produce anything satisfactorily comparable to tuberculin allergy by parenteral sensitization with tuberculin, nor has passive transfer of allergy been very successfully accomplished. For the development of manifest allergy, sensitization with the whole bodies of tubercle bacilli has been necessary. Since the injection of whole dead bacilli does produce allergy, while extracts of the bacilli do not, it would appear that the true sensitizing antigen has not yet been separated from the bacillus by extraction, and that it is a substance different from that contained in extracts or broth filtrates of the bacillus, in spite of the fact that it sensitizes the body to the latter. It is, however, possible that tuberculin injections fail to sensitize because the proper conditions for effective absorption are not provided by brusque injections.

We may remark here that, in contrast to its rapid absorption into

the circulation in the normal body, within certain limits tuberculoprotein is very probably held "fixed" at the site at which it is liberated in the infected body, in a manner comparable to the local fixation of protein antigens at the site of the Arthus phenomenon, as demonstrated by Opie. While this maintenance of local concentration of tuberculoprotein would contribute to the intensity of the local allergic reaction, it is hardly necessary to say that the tuberculin reaction or, indeed, the Arthus phenomenon produced by any protein, is something more than the mere result of the maintenance of a greater local concentration of antigen; for the tissues of the unsensitized animal are, of course, quite unaffected by many more times the amount of antigen necessary to produce inflammation and necrosis in the sensitized body. Since this point has been raised by others, however, we would call attention to the fact that the tissue culture experiments described above show clearly that in spite of being exposed continually to an identical concentration, normal cells survive and grow well for days in amounts of tuberculin which cause the early death of cells from an allergic animal. Inflammation and death of tissue in the allergic reaction are, then, the consequences of a change in the body cells which renders them highly susceptible to damage by contact with tuberculoprotein. The exact nature of this change we are at present unable to define.

What, now, of the fact that tubercle formation in the previously infected body tends to proceed more rapidly than in the normal? One of us has pointed out in another place (70) that accelerated tubercle formation should be regarded only as an accidental result of allergy, rather than as a specific form of the allergic reaction, for local allergic tissue reactions, whether initiated by bacterial or by non-bacterial proteins, are all fundamentally alike, in that they reproduce the standard effects of a chemical irritant upon tissue, *i.e.*, damage to cells, ordinary acute inflammation, and if the amount of antigen be large enough, death of cells. Tubercle formation, however, is a type of reaction which is, intrinsically, completely independent of acute inflammation, as we shall see below. Furthermore, tubercle formation is incited by the lipoid extracted from the bacillus, but this lipoid cannot evoke the allergic reaction. For that, tuberculoprotein is necessary; and although tuberculoprotein calls forth the allergic

inflammatory reaction, it never causes the formation of tubercles. If, however, lipoid happens to be present at the site of action of tuberculoprotein in the allergic body, tubercles will be formed, and formed more rapidly than in the normal body merely because the tuberculoprotein incites, in the allergic body, a more rapid migration of cells to the spot. This manner of regarding accelerated tubercle formation may appear to involve unnecessary hair-splitting, for, assuredly, the acceleration of tubercle formation is directly a result of the chemotactic effects of allergy. But it is actually of considerable importance for a proper understanding of allergy to realize that, fundamentally, all allergic tissue reactions have the same character, regardless of what protein serves as the antigen, and that tubercle formation is in no sense an integral part of that fundamental type of reaction.

VIII. IS ALLERGY, ONCE ESTABLISHED, PERMANENT AND MAINTAINED AT A CONSTANT LEVEL DURING INFECTION, OR DOES IT FLUCTUATE IN INTENSITY AND EVEN DISAPPEAR COMPLETELY?

We have ample evidence that allergy, as tested by the skin reaction to tuberculin, may diminish during active infection to the point that relatively enormous doses of tuberculin fail to produce any more reaction than in normals, and Baldwin, Krause, Willis, Calmette and others have observed marked waning of allergy in animals made resistant by inoculation with bacilli of low virulence. As far as animals are concerned, rabbits react in general more inconstantly, and fluctuations in the intensity of the allergic cutaneous response occur more frequently and sharply than is the case with guinea-pigs. In the human being, we have seen tuberculous patients rapidly lose their skin reactivity to tuberculin, until doses which formerly would have produced a disfiguring slough are tolerated with no reaction. This fact is well known. It has been estimated that 3 to 5 per cent of cases of miliary tuberculosis fail to react to doses of tuberculin larger than one would ordinarily dare to give to a tuberculous patient. Whether allergy, once established, is ever *completely* lost we cannot say. It is said by some that if large enough doses of tuberculin are given, some sort of allergic response can be obtained in every individual who has once been allergic. We have no data bearing on this assertion, but certainly for all practical purposes in routine tests, and as far as the

possibility of the reaction influencing appreciably the type of lesion is concerned, hypersensitiveness may be said to disappear in certain cases, often to return again with renewed vigor. Under what conditions does allergy diminish during progressive infections? Aside from decrease of reactivity during certain intercurrent infections and in the moribund, (the state of allergy in diabetes and in pregnancy needs further study) allergy diminishes especially under conditions of massive tuberculous infection. We have seen allergy wane markedly within 24 hours following injection of large numbers of bacilli intravenously or into the trachea, and in a few human cases of miliary tuberculosis tested every few days we have observed marked fluctuations of allergy.

As an explanation of the diminution of the allergic reaction during massive infection and under other circumstances it has been stated that "in depression or exhaustion states the tissues cannot react typically to any irritant, and therefore they respond only feebly, or not at all, to the application of antigen" (23). Anyone familiar with the frequency of terminal pneumonia in desperately ill and cachectic persons must shy from such an explanation, and besides, that view does not explain why necrosis fails to occur, even if inflammation cannot. It is more probable that the diminution of allergy during massive infection is a desensitization phenomenon dependent upon the combining of most of the available antibody by the large amounts of antigen liberated into the blood stream.

IX. DOES RESIDENCE IN THE ALLERGIC RESISTANT BODY CHANGE THE BACILLUS OF INFECTION SO THAT WHEN INTRODUCED INTO A NORMAL ANIMAL IT PRODUCES A LESION DIFFERENT IN ANY WAY FROM THAT WHICH IT ORIGINALLY PRODUCED?

No. We have observed, in common with other investigators, that bacilli injected into an animal and subsequently recovered from that animal by culture and introduced then into another animal, or introduced directly from the first into the second by means of an emulsion of tuberculous tissue, produce primary and subsequent lesions in the second animal identical with those produced in the first, regardless of the state of allergy or resistance of the first animal at the time when the bacilli are removed, and regardless of the character of the lesion from which the bacilli are taken.

X

It is obvious from the previous sections that, in order to make any forecast about the outcome of a given infection with the tubercle bacillus we would have to know (*a*) the virulence of the infecting bacillus; (*b*) the degree of natural and acquired resistance of the individual; (*c*) the degree of allergy, and, extremely important, (*d*) the size of the infecting dose. We may, therefore, ask: *What is the relative importance of virulence, resistance, allergy and dose as regards* (*a*) *whether or not progressive, spreading infection will occur; and* (*b*) *the type of lesion which will result?*

In the first place, natural, species resistance is a greater protection than is acquired resistance; so much greater, in fact, that human infection with types of tubercle bacilli to which we are naturally resistant is practically unknown. We are concerned here, therefore, only with (*a*) the fluctuating individual resistance to bacilli to which the race is susceptible, different in different individuals, and varying from time to time in the same individual (a totally obscure circumstance, but unquestionably an existing one), and (*b*) resistance acquired through infection. We may express the relative importance of the various factors by saying that, in general, if progressive infection is to be prevented, the degree of *r*esistance (native, individual, and acquired) of the host must equal the product of the *v*irulence of the invading bacilli times their *n*umber, *i.e.* when $R = V \times N$, the invading bacilli will be promptly killed or else their growth will be prevented and they will be encapsulated. But it is only within certain limits that this equation can exist. If the virulence and the numbers are great enough, progressive infection will unfailingly result. This is merely because there is a limit to which acquired resistance can develop. We may, further, express conveniently the relation of the extent of the *l*esion which can be expected to follow infection, to *a*llergy, *r*esistance, *v*irulence and *n*umbers of infecting organisms, by the formula $L \propto \frac{V \times N \times A}{R}$. Obviously, these factors cannot be expressed accurately or numerically in any way, but we have had ample opportunity to observe their interplay, and to realize the general soundness of this schematic expression of their relationship.

As for (*b*), the type of lesion which will result, it is important that in small doses, and in the normal animal, all types of the bacilli, virulent or avirulent, indeed even the "non-pathogenic" acid-fast bacilli such as the grass bacillus, will cause the formation of a fundamentally identical sort of nodular tubercle. This tubercle is formed by mononuclear phagocytes, which may be either blood monocytes, or the phagocytic cells resident in the tissue in question (*e.g.* Kupffer cells).[6] An exudative polymorphonuclear reaction will occur in the normal animal if the numbers of bacilli introduced are large enough (Fig. 1), and this in turn will be followed by tubercle formation (Fig. 7). A few polymorphonuclear leucocytes may appear transiently even when the dose is small, but although they are able to phagocytize the bacilli they take no part in the formation of the permanent tubercle. It is true that in practically all tubercles, a certain number of the constituent cells are derived from the blood, and therefore, in a strict sense, "exudation" plays a rôle in tubercle formation. Furthermore, the development of the tubercle which arises out of the mononuclear cells left at the site of an allergic inflammatory reaction may be difficult to dissociate sharply from the process of inflammation which preceded it. However, we must emphasize that we do not believe that it is in any sense justifiable to confuse acute exudative inflammation with tubercle formation as some would do—*i.e.*, to regard the allergic inflammatory reaction followed by tubercle formation as a single process, differing in no way from slow tubercle formation in the normal body except in intensity and in speed. Acute inflammation is a complicated specific type of reaction, and tubercle formation is a quite separate, different process, regardless of the fact that many of the cells engaged in forming the tubercle may migrate from the blood. It is to be remembered that mononuclear cells are continually wandering into and out of the blood vessels normally, entirely independently of the highly organized proc-

[6] We do not purpose to enter here into the popular discussion of the identity or non-identity of the blood monocyte and the connective-tissue macrophage further than to say that as far as we have been able to observe (and we have been continually conscious of the problem), both of these types of cells, if indeed they can be considered as different types, conduct themselves toward the tubercle bacillus in an identical manner, both *in vivo* and *in vitro*, and we accordingly include them both, without discrimination, under the term "mononuclear phagocyte."

ess of inflammation, so we must not confuse simple migration of cells with acute inflammation. Aside from phagocytosis, the formation of a tubercle is, phylogenetically, the most primitive reaction to an invading organism. The tubercle bacillus, and certain other organisms injected into lower animals below the level at which a vascular, circulatory response can enter in, call forth, before any necrosis, phagocytosis and true tubercle formation, with a central giant cell and surrounding mononuclear phagocytes. The tubercle, therefore, may be considered to be the most primitive *organized* reaction to invading organisms. It is only higher in the scale that the vascular inflammatory mechanism is developed. Acute inflammation involves primarily a vascular reaction and does not imply any tendency to the formation of tubercles. On the other hand, tubercle formation consists essentially in the clustering together of mononuclear phagocytes, and the tubercle requires no acute inflammatory vascular paralysis for its evolution; it can be formed independently of blood vessels in any tissue in which mononuclear phagocytes are present, and indeed, even *in vitro* upon a coverslip in tissue cultures. Furthermore, aside from the fact that we can thus separate acute inflammation from tubercle formation phylogenetically, morphologically and pathologico-physiologically, we are able to separate the body of the tubercle bacillus into two parts, one of which (protein) will provoke acute inflammation in the allergic body, and the other (lipoid), tubercle formation in either the normal or the allergic body. In spite of statements to the contrary here and there in the literature, not once have we seen tubercle formation occur at the site of allergic reactions produced by lipoid-free tuberculins—and we have studied serial sections of many such lesions at periods of from 24 hours to 3 weeks after the injection of tuberculin.

Tubercles may be formed intravascularly or extravascularly. Within the liver lobule, for example, they always arise within the capillaries. If only one or two bacilli lodge at a site, the first step is always phagocytosis of the bacilli, usually by a mononuclear phagocyte (macrophage, Kupffer cell, splenic sinus cell, etc.), although they may be temporarily engulfed by polymorphonuclear leucocytes. This is frequently followed by the enlargement and division of the nucleus of the phagocyte, and by the accumulation of other mononuclear phagocytes about it. All of these clustering cells divide and take on

the appearance of epithelioid cells. The formation of epithelioid cells from mononuclear phagocytes has been demonstrated conclusively by Lewis, Willis and Lewis (51), Sabin, Doan and Cunningham (71) and others, and we have confirmed the fact repeatedly in our studies with vital stains. The original phagocyte, which by its swelling and nuclear division may appear as a giant cell, is usually killed, and the giant cells of the fully formed tubercle arise from similar changes (or by fusion with their neighbors) in the surrounding mononuclear cells which have come either from the blood or from the tissues. In spite of the most painstaking search for several years, we have never seen anything requiring the interpretation that ordinary capillary endothelium anywhere in the body gives rise to any of the cells of the tubercle. It is remarkable that in the foremost German textbooks of pathology there still occurs the primitive idea that parenchymatous *epithelial* cells become transformed into the epithelioid cells of the tubercle. This error arose from a misinterpretation of the early observation of mitoses in the regenerating parenchyma about tubercles in the liver and elsewhere. The sum of the most careful and reliable work is entirely against the participation of any epithelium in tubercle formation except in one organ—the lung—where the old debate as to the phagocytic activity of the alveolar epithelium makes it impossible to speak with absolute certainty about the origin of all of the cells of the pulmonary tubercle, although most of them are undoubtedly mononuclear phagocytes, as has been demonstrated by Lewis, Willis and Lewis (51). The careful recent work of Gardner and Smith (52) and of Foot (53) repudiates the idea that the alveolar epithelium participates in any way in intra-alveolar phagocytosis.

Although it is true that, aside from massive experimental first infections, necrosis of tuberculous lesions does not appear until allergic hypersensitiveness to the bacillus is established, it is not a sufficient explanation of the caseation of tubercles to say merely that "tubercle bacilli are necrotizing for the tuberculous, allergic animal." Allergy alone cannot explain this necrosis. Either fresh, minute tubercles or older, very large ones formed in animals (or patients) which were highly allergic at all times during their development may show either extensive necrosis or no necrosis at all. A sufficient number of bacilli are essential for necrosis of any appreciable extent. Unless large numbers

of bacilli lodge at the site originally, or unless the lesion is initiated by a few bacilli which multiply until considerable numbers are present, or, finally, unless the lesion is initiated by necrotic debris saturated with the tuberculoprotein of large numbers of disintegrated bacilli (*e.g.* aspiration of such material from a cavity), caseation will not occur. Numbers of bacilli are, therefore, of prime importance. The extent of necrosis in tuberculous lesions will always be a result of the balance between the degree to which allergy is developed and the local concentration of the bacillary products. The number of bacilli necessary to effect necrosis will, in general, be inversely proportional to the degree to which allergic hypersensitiveness is developed, but even with very active allergy the number must be more than a mere few. This we have repeatedly observed in our experimental inoculations, and we shall have occasion to point out the bearing of this fact upon the explanation of the much debated lesion which characterizes acute caseating miliary tuberculosis.

Certainly, we agree with Krause in being completely unable to subscribe to the familiar idea that the necrosis is the result of the lack of blood supply in the centre of the tubercle, for a very large tubercle may have no necrotic centre, and very small ones may be completely necrotic—even tubercles so minute that the entire mass lies within a liver sinusoid. Furthermore, it is not at all uncommon to see numerous lymphocytes wandering into the freshly necrotic centre of a tubercle. If there are crevices large enough to permit lymphocytes to crawl into the avascular centre, surely nutrient fluids could trickle in.

That necrosis in tuberculosis may occur entirely independently of the allergic inflammation is obvious from the tissue-culture experiments of Rich and Lewis described above (8), and also from the fact that caseation of the avascular centres of large tubercles is common. It is therefore difficult to agree with Krause that necrosis "will always be found (when it occurs) to be an end result of the inflammation with which the allergic reaction is initiated" (2). Necrosis is often merely the direct result of the contact of hypersensitive cells with tuberculoprotein, and needs no preliminary or accompanying inflammation to usher it in.

As the tubercle grows older, there occurs the production of *fibrous*

tissue, beginning usually at the periphery where there are fewer bacilli. The origin of this connective tissue has always been a perplexing question. Does it grow in by proliferation of surrounding fixed connective tissue? Do specific "fibroblasts" wander in and lay down fibrous tissue? Or are mononuclear phagocytes really able to form connective tissue, as Maximow (54) and others believe? At present no one can say with certainty. However, there is one thing about the matter which seems important to us: reticulum is laid down in tubercles before fibrous tissue. We have frequently observed that in spite of the chemical differences between reticulum and connective tissue, the former often passes over very gradually but very surely into the latter. Our own attention was first drawn to this some years ago in the study of the reticulum in a case of Gaucher's disease, but the transition is no less striking in tubercles, or in any reparative process such as that in cirrhosis of the liver, if the tissue be stained for reticulum and for connective tissue. Miller (55), Foot (57), and others have commented upon this transition of reticulum into connective tissue, and Mallory (56) has recently directed especial attention to it. We are able to confirm the observations of these investigators in every respect. The present problem is, therefore: what forms the reticulum of the tubercle? For we have no doubt that these fibers can pass over into connective-tissue fibres. By means of Foot's invaluable method (58) reticulum can be easily demonstrated in very small tubercles which appear to consist entirely of epithelioid cells (mononuclear phagocytes). Can these cells form it? We have repeatedly seen, in common with others, that, in tissue cultures, mononuclear phagocytes can assume the shapes of "fibroblasts," develop fibre-like prolongations, and form a compact tissue. It is of very great interest and importance that Maximow (54) has just reported that he has been able to demonstrate the appearance of reticulum and collagen fibrillae in tissue cultures of the mononuclear phagocytes of the blood. It is entirely possible that these wandering phagocytes may be able to form connective tissue by first laying down reticulum, and confirmation of Maximow's work would be of the most fundamental importance to the general problem of repair.

So much for the response of the normal animal to moderate doses of bacilli. Neither virulence of the bacilli nor natural resistance interfere

with the general character of tubercle formation. Numbers, as we have seen, may modify it, and so does allergy, the effects of which we have already discussed. It is important, however, to point out that when we look at proliferative lesions, we may be completely unable to say with certainty whether they developed under the influence of allergy or not; for inflammation may be inconspicuous or absent in foci established by a few bacilli in the allergic animal, and there is, of course, no way of determining whether the lesion has developed with unusual rapidity or not. It is to be remembered, furthermore, that the immediate allergic inflammatory reaction is often followed by a proliferative process ending in the formation of tubercles, in fibrosis, or in the encapsulation of necrotic debris.

As regards this scarring and encapsulation, we do not believe that the widely accepted concept of the existence of a specific form of granulation tissue in tuberculosis (so-called "tuberculous granulation tissue") is a profitable one. The sequence of events leading to the formation of connective tissue in the avascular tubercle is, of course, quite different from that occurring in ordinary scar-tissue formation; but we believe that the granulation tissue leading to the formation of the connective tissue wall of a cavity, or to the encapsulation or replacement of necrotic, caseous debris, is in no sense different from that forming the wall of an abscess, or that encapsulating or replacing an infarct, except in that it is generally 'secondarily infected' with the tubercle bacillus. In other words, *repair* in tuberculosis is no different from repair elsewhere, except in so far as it is interfered with by the infection. This is a different concept from that assuming a special form of repair ("specific tuberculous granulation tissue") in tuberculosis. The tubercle is not to be confused here. It is in no sense a form of repair. It may develop in man and animals before a single cell has been destroyed. We believe that if one produced an allergic reaction with caseation in an ordinary granulating wound, or indeed, merely infected a granulating wound with tubercle bacilli, it would be quite impossible to distinguish the result from the so-called "specific tuberculous granulation tissue." We have not been able to convince ourselves of the existence of the alleged greater vascularity, or of any other criterion of "tuberculous granulation tissue," and we regard scarring in tuberculosis as merely the standard attempt of the body to

repair destroyed tissue with connective tissue, modified in appearance only by the fact that, being adjacent to tuberculous foci, it is infected with tubercle bacilli, and its progress retarded or thwarted by the necrotizing effects of allergy.

XI. WHAT ARE THE POSSIBILITIES AS TO THE FINAL OUTCOME OF THE TUBERCLE?

1. The bacilli may all die out, and the whole become converted into a hyalinized mass. If there has been central necrosis, the necrotic tissue may become calcified, or even ossified with attendant marrow formation.

2. The bacilli may remain alive in the centre, encapsulated by a wall of hyaline scar tissue.

3. The tubercle may undergo widespread necrosis, with spread of the proliferating bacilli to the surrounding tissues.

4. The tubercle may resolve and be completely absorbed, leaving no trace. This can occur only before connective tissue appears, but that it can and does occur is unquestionable. We have frequently observed this remarkable phenomenon, which is especially striking in the liver where, after a loosening up and separation of the epithelioid cells, they leave the spot, and a small cavity remains through which (because the tubercle began originally in a sinusoid) blood flows. Liver cells flattened by pressure atrophy bound the little cavity. Every stage can be seen up to restitution of the lobule without scarring (Figs. 10, 11, 12, 13). This resolution is apparently neither preceded by, nor accompanied by necrosis. It is as though, all the bacilli having been done away with by digestion, the cells have no further stimulus to cling about each other, and simply separate and wander off. The bearing of this phenomenon upon "disseminated tuberculosis" will be obvious when we discuss that condition.

XII. WHAT ARE THE POSSIBILITIES AS TO THE OUTCOME OF THE ALLERGIC INFLAMMATORY REACTION?

1. If it is mild and all bacilli are killed, the inflammatory exudate may be completely absorbed and the site restored to normal. This is true even of patches of tuberculous pneumonia, as we shall see below.

2. If the reaction is mild and bacilli are left alive at the site, much of

the inflammatory exudate is absorbed, but a tubercle or a group of tubercles proceeds to develop about the remaining bacilli.

3. The reaction may be initiated by a large number of bacilli and may be accompanied by extensive necrosis. In such a case, if many bacilli are left alive, a spreading, progressive lesion results, with abortive peripheral attempts at tubercle formation and repair which are continually thwarted by the extension of the allergic necrosis. If all of the bacilli die, the necrotic area will be subsequently encapsulated by a wall of connective tissue which, during its formation, will have the appearance of ordinary granulation tissue. Between these two extremes there may be found every degree of partial or complete connective-tissue encapsulation, and every degree of tubercle formation in the encapsulating wall, depending upon the number of bacilli that remain alive in the necrotic mass and infect the periphery.

We have said that the most prominent immediate reaction of the uninfected animal tends to be the proliferative tubercle, and that of the allergic animal an exudative inflammation; and this is in agreement with the best American work. However, it is necessary to state that certain French and German workers (for example, Aschoff, Meyenberg, Huebschmann) state emphatically that the first response of the normal individual is an exudative inflammation; and some (among them Marchand) decry all attempts to classify the lesions as "exudative" or "proliferative," since one form may shade gradually into the other. From our own observations we are convinced (*a*) that, unquestionably, with the proper dose properly placed, either the allergic or the non-allergic body can be made to react with either exudative inflammation or tubercle formation, but that, for reasons given in sections VI and VII, the allergic body has a markedly greater *tendency* to react exudatively than has the non-allergic one; (*b*) that any absolute and dogmatic distinction between the types of lesions developing under these two states of reactivity, such as is advocated by certain investigators, is unwarranted; and (*c*) that the terms "exudative" and "proliferative" are very useful for the description of what we see in any case, but dangerous if used as catchwords, or as synonyms for states of resistance.

XIII

Miliary tuberculosis offers so wonderful an opportunity to study the early reactions to the bacilli under different local and immunobiological conditions that it is important to consider certain questions regarding the pathogenesis of this process before we proceed to the analysis of individual tuberculous lesions. *Is miliary tuberculosis always produced in the traditional manner, i.e. by the sudden rupture of a tuberculous focus into a large blood or lymph vessel? Do the different sizes of tubercles seen in a single case indicate successive "showers" of bacilli, resulting from successive sudden eruptions of such foci into vessels?*

We answer both of these questions in the negative.

In the first place, let us ask ourselves what we mean by "miliary tuberculosis." Given a progressive tuberculous lesion anywhere in the body, different cases show at autopsy different degrees of haematogenous infection of the viscera, varying from a sparse scattering to the most profuse studding of the tissues with small tubercles. The latter situation everyone admits to the category of miliary tuberculosis; but what of the other extreme—the cases in which, say, only a single tubercle is found on careful microscopical search throughout several sections two centimeters square? In other words, are we to consider as miliary tuberculosis every haematogenous dissemination of bacilli, following which a scattering of tubercles can be demonstrated in the tissues? And if not, since in different cases one finds all imaginable gradations between very few scattered tubercles and myriads of them, just how many tubercles per microscopic field shall be necessary for the diagnosis of miliary tuberculosis? Aside from the bearing of this matter upon the evaluation of statistics concerned with the relation of macroscopic vascular involvement to miliary tuberculosis, we have placed this somewhat scholastic question chiefly to emphasize the fact that it is quite impossible to draw a sharp line between the sparse scattering of tubercles which ordinarily occurs during progressive tuberculosis of any organ, and the greater number generally spoken of as miliary tuberculosis. This fact is important for the reason that no one would presume to insist that the caseation of large, macroscopic vessels should be invoked to explain the presence of a few scattered visceral tubercles; and since all degrees of visceral infection occur, it becomes

impossible to define the exact point at which macroscopic vascular erosion enters as a causal factor. In other words, we believe that even extreme miliary tuberculosis can occur in the absence of such gross vascular involvement. A sudden, acute massive miliary tuberculosis is undoubtedly invariably associated with the sudden eruption of a caseous focus into a macroscopic vessel. But there exists a more insidious form of miliary tuberculosis in which bacilli, entering the blood stream through microscopic vessels in a lesion, colonize here and there in the tissues, with an especial tendency to perivascular localization; and these new lesions in turn discharge eventually into the adjacent microscopic vessels, from which gradual dissemination still new foci arise; until, at length, myriads of minute discharging foci, the cumulative result of such progressive infection, create the pathological picture of frank miliary tuberculosis. It is thoroughly clear from acid-fast stains of our experimental and autopsy material that the bacilli do very commonly find their way into the blood stream through such involvement of microscopic vessels (Figs. 14, 15, 16); and it is to be remembered that the intimal tubercles found in large veins are themselves the results of haematogenous infection.

Miliary tuberculosis must be regarded as nothing more or less than the result of a septicaemia with the tubercle bacillus. One does not strain to find a large vein ruptured as a cause of the pyogenic septicaemias; one is content with a focus produced subcutaneously by a pin-prick. If an entire lymph node were found converted into an abscess in a case of septicaemia, no one would hesitate to incriminate that node as the probable focus of origin of the blood-stream infection. But a score of freshly necrotic tuberculous nodes, swarming with bacilli and continually perfused by the lymph and blood streams (Fig. 18), are ignored as possible foci of origin of blood-stream infection in miliary tuberculosis, and hours will be spent in the search for a rupture into a large vein. If the rupture is not found, one is supposed to feel a sense of guilt and to be ashamed of poor technique. Since the famous and then striking work of Weigert (36), the tubercle bacillus has come, for no sensible reason, to be regarded as different from all other organisms in that it is popularly supposed that it does not infect the blood stream in the usual manner (*i.e.*, by entrance of bacilli through microscopic vessels in an infected area), but that a large mass must suddenly ulcer-

ate into a vessel and discharge cheese, bacilli and all into the circulation, thus producing a single "shower" of tubercles in the various organs. Everything speaks against such a view. Thirty years ago Benda (37) and others maintained that many cases of miliary tuberculosis cannot be explained on such a basis, and all information acquired since supports the correctness of their objection. In the first place, it is a perfectly well known fact that tubercle bacilli may be cultivated repeatedly, at different times, from the blood of patients with miliary tuberculosis—nay, even from the blood of patients with progressive tuberculosis of any organ without miliary tuberculosis. On the basis of the 'shower' theory, the venipunctures would have to be remarkably timed with the 'showers' in order to obtain a positive culture, for we know that tubercle bacilli, or any other foreign particles for that matter, if suddenly injected into the circulation, are cleaned out of the blood in a very short time. The presence of bacilli continually in the blood indicates one or more continually discharging foci. Indeed, so far from being a blood-stream infection for which a single eruption from a single focus is responsbile, a *progressing* case of miliary tuberculosis is, perhaps, more than any other type of septicaemia, the result of repeated discharges of bacilli from many foci. This is the effect, largely, of the tendency to the perivascular localization of tubercles (Fig. 14); and because of the chronicity of the condition, time is provided for the extension of such foci into the blood stream (Figs. 15, 16). That miliary tuberculosis, once established, is practically never recovered from is not infrequently the result of this continual progressive infection of small vessels. It is a self-propagating septicaemia, very soon progressing independently of the original focus, and the original focus may be a spreading, caseating lesion within an organ, which infects myriads of small vessels as it progresses, quite as well as the more dramatic discharge of bacilli and caseous material into a large vessel. It is far from true that either small or large vessels infected by the tubercle bacillus quickly become obliterated. That process is usually a slow one requiring weeks in most cases, as witness the rarity of this form of vascular occlusion in the heavily infected vessels of the meninges in tuberculous meningitis. We attribute any obliterative endarteritis of the large vessels in pulmonary cavities more to the loss of tissue than to the direct effect of the infection. This is merely

an application of the general principle that when an area of any organ ceases to require blood either because of loss of parenchymatous tissue or because of cessation of function, the supplying vessels usually become obliterated. This process is familiar in chronic glomerular nephritis, in hydronephrosis, in the senile uterus, etc. If the vessels in a tuberculous area are ruptured by caseation of their walls, secondary thrombosis will, of course, occur.

In support of the theory that miliary tuberculosis is always caused by the sudden discharge of a caseous focus into a large vessel, it is commonly stated that the tubercles scattered through the various organs are either all of one size, indicating a single discharge, or else that they are of several sharply different sizes, representing several different and successive sudden eruptions of large foci into the blood-stream. In regard to finding all of the tubercles of a uniform size in any organ in well-marked miliary tuberculosis, we may say that our microscopic studies have convinced us that this must be an exceedingly rare condition, if indeed it ever does occur. Certainly in our material it is the rule that tubercles of different sizes are present in each organ involved. It is, however, sometimes possible to separate these tubercles into, say, three or four more or less sharply defined sizes, and it is this which has led to the belief that they represent the results of different or successive sudden discharges of bacilli into the blood-stream. But sudden, massive discharges of bacilli at different intervals are not necessary to produce the picture of a body studded with tubercles of sharply different sizes. We have repeatedly produced this picture by a single injection of bacilli in the blood-stream. All of the bacilli are cleaned out of the blood in a very short time, but the number of bacilli stopping at each site is not always the same and the organs of such animals examined a week or two later will show not one 'crop' of tubercles of approximately the same size, but, in each organ, tubercles of several different sizes and ages (Figs. 14, 17); and with little effort, infection of minute (microscopic) vessels by adjacent tubercles, or by tubercles developing in their walls, can always be demonstrated. Indeed, with this in mind we made a very offhand survey of a *single section* of lung in 46 human cases of miliary tuberculosis, and in 20 of these cases we found microscopic involvement of blood-vessels of a character permitting discharge of bacilli into the blood. Thus it is a

fact that small lesions in the neighborhood of minute vessels do frequently discharge into the blood-stream (Figs. 15, 16). What reason then to demand invariably a macroscopic vascular involvement as a cause of the septicaemia, when we know that blood cultures prove the discharge of bacilli into the blood stream from chronic caseous foci *before* the widespread infection manifested by clinical and pathological miliary tuberculosis appears, and that there is a marked tendency to infection of myriads of microscopic vessels during tuberculous bacillemia? Huebschmann is inclined to regard thoracic duct tuberculosis in miliary tuberculosis in much the same light, *i.e.*, as secondary to the septicaemia; and indeed the marvel is that the thoracic duct is not infected in every case of miliary tuberculosis, with the tissues and fluids teeming with bacilli and the lymph stream so sluggish.

We are perfectly familiar with miliary tuberculosis produced by the sudden discharge of a caseous mass into a large vessel and we shall discuss the peculiar clinical and pathological effects of this condition below (Section XV). We are stressing here merely the fact that such gross vascular involvement is by no means necessary for the development of miliary tuberculosis, and this is especially true in children before the development of a high degree of resistance. We may mention in this connection that the finding of an intimal tubercle within a large vessel should never be lightly accepted as the site of origin of a miliary tuberculosis, for most intimal tubercles are circumscribed and covered over with endothelium and do not discharge large numbers of bacilli into the blood. We have laboured this point of the manner of origin of miliary tuberculosis for the reason that, in spite of the advance in the understanding of septicaemias and of tuberculosis, the Weigert doctrine continues to be propagated, and to cloud the understanding of certain cases in a manner which we shall discuss below. The factors determining the development of frank miliary tuberculosis as contrasted with sparsely scattered, disseminated tubercles will be discussed in the next section.

XIV

There is a final matter of a general nature to be considered before we discuss specific tuberculous lesions, namely—*what principles are involved in the long recognized difference between the effects of tuberculous infection in the adult as contrasted with the infant and young child?*

Numerous conflicting answers to this question have been offered by different investigators. We shall examine certain of these views, and we shall attempt to show that the question may be answered without recourse to speculations unproved by experiment.

In the first place, what are the chief differences observed in autopsies upon tuberculous children (always including infants) and adults? Emphasizing that there occur important exceptions to each of the following generalizations, we can say that the most noticeable differences in any unselected series of cases are (*a*) a tendency to a more extensive involvement of lymph nodes in children; (*b*) a greater tendency to fibrous encapsulation and to healing of lesions in adults; and (*c*) a greater tendency in children to the rapid spread of lesions, and to the development of miliary tuberculosis. Minor differences in various organs need not be mentioned here. The results of these tendencies are easily recognized in most cases of tuberculosis in adults and in children. The problem then is merely: to what are these tendencies due?

First of all it is important to state that, *so far as is known*, there is no inherent difference between the normal bodies of children and of adults which might account for the observed differences in reaction to the bacillus. On the one hand, it is well known that adults from uninfected regions are, when exposed to the tubercle bacillus, ravaged by a type of tuberculosis which has the characteristics of that which we are accustomed to see in children. On the other hand, we are quite familiar with the occasional cases of tuberculosis in children, in which the process is exactly like that characteristic of adults,—lungs, for example, which with their encapsulated cavities and marked fibrosis appear for all the world like miniatures of the chronic phthisis of adults. Finally, the most careful investigations have failed to prove that the reaction of normal young animals to the bacillus is different in any way from that of adult animals (25). It is possible that the last word on this question of age susceptibility has not yet been spoken, but the evidence available at present is entirely against the view that age difference, in itself, is a factor of importance in the development of these two broad types of tuberculosis. What then are the determining factors? We shall first examine the explanations which have been offered by such year-long students of the matter as Ranke and Krause. We may say

that Aschoff and many Germans subscribe entirely, or partially, to the explanation of Ranke, and most American and certain French investigators to that of Krause.

Krause would make the differences between tuberculosis in the adult and the child a result of three factors: (*a*) the degree of allergy; (*b*) differences in the lymphatic systems of adults and children; and (*c*) differences in the character of the connective-tissue investment of lesions. Briefly, he believes that allergy is greatest in the young child (*i.e.*, shortly after the primary infection) and that it diminishes as time passes, so that it is at a much lower level in adults. Since he believes that "immunity is achieved through allergy," it follows that he believes that the infected child possesses a greater acquired immunity than does the infected adult. But this greater acquired immunity of the child he believes to be counterbalanced by (*a*) the supposed fact that an infant cannot form connective tissue under any circumstances as well as an adult can; therefore, the lesions in the former are poorly encapsulated; and (*b*) the supposed fact that whereas the lymphatics of the child's tissues are wide open, unobstructed channels, the lymphatics of adults, as a result of all sorts of slight infections, etc., become greatly obstructed and transport of bacilli is inhibited. Thus, in spite of its greater acquired resistance following infection, the two latter circumstances favor, in the child, more easy spread of bacilli not only locally by extension but also by lymphatic transport to regional nodes. Both the infected adult and child possess the acquired power to 'fix' the bacilli locally and so retard their spread, but since the adult adds obstructed lymphatics to this fixing mechanism, drainage of bacilli to lymph nodes is less in adults and the involvement of adult lymph nodes therefore less. Krause mentions as a further factor favoring the spread of tuberculosis in early life the fact that since all lesions in infancy are of recent origin, fibrosis about any given focus is less complete than it would be some years later. This, however, has no bearing upon the question before us, for, of course, the adult with progressive tuberculosis has also many entirely fresh lesions resulting from endogenous reinfection.

We offer the following objections to Krause's view: First, we do not believe that the facts warrant the statement that the infected child has an acquired resistance greater than that of the infected adult, acquired

resistance here being taken to mean the opposition of the body to the life and multiplication of the bacilli, as Krause and everyone else interprets it. Although infected adults as a class may give weaker tuberculin reactions than infected children, we have already pointed out that the statement that the intensity of the tuberculin reaction is a measure of the degree of resistance is quite gratuitous. We need only recall the clean-cut experiments of Willis (46) in which animals with practically no allergy were nevertheless highly resistant. Now the fact that infected children, with all their tendency to spreading tuberculosis, give brilliant tuberculin reactions, is difficult to reconcile with the view that allergy is a measure of acquired resistance, and it becomes necessary for those who believe that it is to seek for other factors which can be interpreted as hampering the action of the infected child's assumed higher degree of resistance. We are given, therefore, the two above explanations. Let us examine these explanations more closely.

In the first place, as to the poorer ability of the young child to make connective tissue, one could point to the prompt healing of the cut umbilical cord, to the great amount of scar tissue often seen in chronic empyema, to the dense strictures of the oesophagus following the ingestion of lye, etc., as evidence that scar tissue can be formed in abundance and promptly in infants, providing that there is nothing to prevent it. Surgeons are unanimous in agreeing that operative wounds in infants heal distinctly more rapidly than in adults. Furthermore even the "primary" tuberculous lesions found in the lungs of infants and young children are themselves often densely encapsulated with connective tissue. Indeed, the heavily encapsulated gummata in premature, stillborn infants with congenital syphilis demonstrate plainly enough that connective tissue can be formed abundantly even *in utero*—and rapidly, for the lesions of congenital syphilis are said never to begin before the sixth month of intrauterine life. Offhand, one would suppose that the greater growth energy of the child's tissues would favor rather than depress reparative processes, and, indeed, the careful experimental studies of Maximow (27) on the development of scar tissue have shown that this is actually the case. Maximow embedded little celloidin chambers in the tissues of the abdominal wall of adult and newborn animals and followed the reaction about them from day to day. He found that "in principle aseptic inflammation

and scar formation proceed in newborn animals exactly as in adults, except that the processes in the newborn occur at a more rapid rate. . . . . At the end of four days all of the more impetuous processes have entirely ceased, and the encapsulating tissue has approximately the same appearance as that observed in adult animals at the end of fifteen days." These considerations prevent our acceptance of the statement that infants are "deficient in . . . . their ability to react fibrously to irritations and injuries of all kinds" (26).

But regardless of all this, we cannot be impressed by the idea of the importance of connective tissue as a primary factor in checking the progress of a lesion for, after all, the encapsulation of the bacilli by connective tissue is not the important means of restraining their growth. The formation of a connective-tissue encapsulating wall is a *result* of resistance rather than a cause, *i.e.*, it is purely a reparative process, and will always be formed if, and when, the bacilli cease to propagate rapidly; and, although the idea may appear radical because of the great stress universally laid upon fibrous encapsulation, we question seriously the efficacy of a few millimetres of connective tissue as a barrier able to restrain the proliferation of the organisms. This skepticism may be realized to be not entirely unwarranted if one pauses to consider the manner in which even solid bone crumbles in the face of vigorously multiplying tubercle bacilli. It is, of course, obvious that when quiescent bacilli have become encapsulated, their spread from that site to another will be mechanically interfered with; but were those enclosed bacilli not held in an inactive state by acquired resistance the connective tissue about the lesion would be rapidly destroyed. If it be suggested that the connective-tissue wall prevents multiplication of the organisms by preventing inward diffusion of nutriment, one can easily parry by questioning how it comes about, then, that the products of the bacilli diffuse *out*, as they must, or else the fundamental idea of the maintenance of acquired resistance by the persistence in the body of a walled-off, tuberculous focus containing living bacilli would become senseless. Indeed, we know that diffusion into gummata must occur, for otherwise iodides would be quite unable to effect their resolution; and gummata are, characteristically, much more heavily encapsulated than tuberculous lesions. And, finally, with how little conscience everyone disposes of this supposedly formid-

able connective tissue barrier in describing the spread of infection! "The individual becomes 'run down,'" say even those who respect the connective barrier most, "his resistance is lowered, the bacilli break through the connective tissue wall, and infection extends to the tissues about the focus." *Now this is exactly what does happen, and happen repeatedly.* It is an exact statement of fact, even though the meaning of 'run down' and 'lowered resistance' cannot yet be completely understood. Neither the connective-tissue wall, nor any other tissue, is of any consequence as a check to a sufficient number of virulent bacilli *when resistance becomes lowered.* The essence of the resistance question seems to us to lie not in the ability of the body to form connective tissue about the bacilli, but in the inability of the bacilli to propagate freely in the particular body in question; and, as we have said in discussing virulence and resistance, we believe this to be dependent upon the immediate condition of the body fluids and cells, whether possessed naturally, acquired through infection, or lost under debilitating circumstances. If, actually, the formation of connective tissue were of fundamental importance in preventing the growth of the bacilli, and if in early life the ability to form connective tissue were really less than in later life, newborn animals should develop more extensive lesions after infection than adult ones; but, as we have said, this is not the case. In short, for reasons which we shall state below, we believe that less connective tissue is formed about progressing childhood tuberculosis because the bacilli are multiplying more rapidly and the lesions spreading more rapidly than in the average adult case, and that consequently the opportunity for repair is diminished; not that the bacilli multiply rapidly and the lesions spread rapidly because the child cannot form connective tissue properly or has not had time to do so. In place of Krause's aphorism that "the patient is as resistant as the shell of his tubercle," (23) we believe that the patient is as resistant as his acquired ability to hold in check the growth of tubercle bacilli.

Finally, as to the degree of obstruction of the lymphatics in the adult as compared with the child, we are skeptical also about the importance of that in the matter. We have no doubt that, as age progresses, focal inflammations may obliterate a lymphatic channel here and there, and senile atrophy unquestionably strikes lymph nodes as well as all other organs. It is clear, further, that very considerable lymphatic obstruc-

tion must occur in special conditions, such as emphysema, for example. But that the average young or middle-aged adult has his lymphatics so obliterated that easy drainage is not possible, we cannot believe for a moment. Too many facts are opposed to it, even aside from Reichert's beautiful demonstration of the prompt regeneration of obstructed lymphatics (69). It is perfectly familiar, for example, that the sinuses of the bronchial nodes in adults with ordinary pneumonia are flooded with cells and debris, and the same is true during acute tuberculous pneumonia; similarly, the contents of the distended sinuses of adult mesenteric nodes during typhoid or other ulcerative intestinal processes offer eloquent evidence of the patency of the associated lymphatics; and such examples could be offered in abundance for every region of the body (Fig. 29). Furthermore, the fact that aboriginal adults on their first contact with the bacillus develop the "childhood type" of tuberculosis with the characteristic lymph node involvement (Aschoff and many others), even when such adults come from the desert where there is abundant opportunity for inhalation of irritating dust, is itself obvious evidence that the mechanical obstruction of lymphatics in adult life must play little rôle in preventing spread to regional nodes. The bearing of this reaction of the aboriginal adult upon the theoretical difference between adult and child in ability to form connective tissue, and so to prevent spread of bacilli is also obvious. Indeed, in the face of the deplorable ease of transport of large cancer cells to lymph nodes in adult life, it seems highly unlikely that simple obstruction could account for the lack of spread of tubercle bacilli. We shall return to this general question below.

Krause, further, in his widely quoted Harvey Lecture (29), supports his argument of lymphatic obstruction by a comparison between the localization of tuberculous lesions in the lung of adult and child with that in the lung of rabbit and guinea-pig, respectively. Tuberculosis tends to localize all through the rabbit's lung, with little bronchial node involvement (adult type), whereas the guinea-pig's lung is relatively spared and the lymph nodes at the hilum are heavily infected (childhood type). Now it happens that the rabbit has considerably more lymphoid follicles in the substance of the lung than the guinea-pig, and the lesions tend to localize in this intrapulmonary lymphoid tissue, so that the bacilli are presumably filtered out at these sites before they

can reach the hilum, and the nodes are therefore relatively spared. The amount of lymphoid tissue increases, in the human lung, with age, and Krause adds this fact to his idea of obstructed lymphatics as an explanation for the escape of the hilum nodes in adults.

Although this comparison between the localization of tuberculosis in the lung of the rabbit, guinea-pig and human being is attractive and plausible on the surface, there are numerous considerations which prevent us from believing that the lymphatic conditions within these animals' lungs really throw light upon the localization of tuberculosis in the lung of man at the different periods of life. In the first place, the lung of the human being does not approximate the anatomical condition of the rabbit's lung as regards the extraordinary richness in lymphoid tissue. It must be understood that the lungs of the rabbit are remarkable in that they are studded with innumerable lymphoid follicles which are so strikingly well developed that Krause writes that "there can be little doubt that not a few observers have regarded them as pathological formations: I may avow the same error when I first came across them" (29). In direct relation to this condition (and again entirely different from what holds for the human being) there is the fact that the tracheobronchial lymph nodes draining the rabbit's lung are so insignificant in size that Willis states that in about 20 per cent of the rabbits examined they could be found only by microscopic examination, and that they may even be entirely absent or unrecognizable (28). In other words, it is clear that the lymphoid tissue draining the rabbit's lung is distributed normally *within* the lung itself, instead of being collected, for the most part, in the form of nodes outside of the lung, as it is in man. There is, furthermore, an anomalous condition pertaining to the pulmonary lymphoid follicles of the rabbit which greatly favors infection of this tissue in comparison with that in the guinea-pig and in man, *i.e.*, in the rabbit the intrapulmonary lymphoid follicles are supplied by the *pulmonary* artery, whereas in the guinea-pig (30) and in man (31) the much scantier and less well developed intrapulmonary lymphoid foci are supplied by the bronchial artery. Obviously, the opportunity for metastatic haematogenous infection of this tissue in the rabbit is greatly furthered by this fact. "This has an important bearing on experimental work which involves the lung of the rabbit," writes Miller, who made the discovery, "for

any microörganism that is introduced into the venous circulation of the rabbit is conveyed from the right side of the heart directly to these masses of lymphoid tissue by the pulmonary artery" (32). In the light of such fundamental differences between the regional pulmonary lymphoid tissue of the rabbit and that of man, we cannot but feel that it is rash to explain the pathogenesis of adult human pulmonary tuberculosis on the basis of the readiness with which this tissue becomes infected in the rabbit.

As a matter of fact, there is very good evidence that the normal lymphatic anatomy of the human lung at different age periods is of little importance in determining the distribution or character of tuberculous involvement, or the degree to which the regional nodes will be involved. We may recall again the fact that aboriginal adults on first exposure to the bacillus develop the type of progressive tuberculosis characteristic of childhood with prominent involvement of the regional lymph nodes. This would not be the case if the normal increase in pulmonary lymphoid tissue in adult life really rendered the adult's lung comparable to the rabbit's in the matter of holding bacilli from the regional nodes. Finally, if the interposition of foci of lymphoid tissue were really a strong enough barrier to prevent infection of regional lymph nodes, this should be effective as a general principle in any region of the body. If, however, we turn to the intestines, which are very rich in lymphoid follicles, we find that these follicles are especially well developed in children, very commonly being relatively much more prominent than one observes in adults, and certainly always far more extensive than any adult lung ever contains; yet tuberculosis of the intestines in children is regularly associated with great enlargement and caseation of the mesenteric *nodes*, whereas in adults the changes in the nodes draining tuberculous intestinal ulcers are as inconspicuous as are those in bronchial nodes draining adult pulmonary tuberculosis. And here, again, the aboriginal adult meeting the bacillus for the first time develops the "childhood type" of extreme involvement of mesenteric nodes. We shall not dwell upon these matters further, but from the above considerations it may be gathered why we do not find Krause's explanation of the differences between adult and childhood tuberculosis satisfying.

Let us now compare it with Ranke's explanation. Ranke (59)

divides tuberculous infection into three successive stages, somewhat analogous to those of syphilis: first, the stage of the primary infection; second, the stage of hypersensitiveness and low resistance, with a consequent tendency to rapid spread of lesions; this is the period of childhood tuberculosis; and third, the stage of high resistance (adult tuberculosis). Aside from certain differences in terminology, we find that whereas Krause states that the infected child has more acquired specific resistance than the adult, Ranke states exactly the reverse. Ranke bases his argument in general upon the fact that childhood lesions are usually more rapidly progressing and destructive than adult lesions; therefore, the child is in a state of hypersusceptibility and the adult in a state of greater resistance. The basic difference really lies in the interpretation of caseating lesions. To Krause and others, caseation is a result of the allergic reaction, and the allergic reaction is an immunity reaction; therefore, caseation is a sign of resistance. Tissue is destroyed but bacilli are killed in the process. Not so for Ranke and his followers. Tissue undergoes caseous necrosis not in connection with any immune reaction, but because the body has little resistance and is hypersusceptible to the products of the bacillus. Marchand and Herxheimer state also, along the same line, that caseous pneumonia, for example, is not a defense reaction, as Krause and Aschoff believe, but is purely a harmful affair associated with insufficient resistance. We have already given our reasons for being on our guard against interpreting the allergic response of the tissues in terms of resistance.

We believe that the division of tuberculous infection into three stages comparable to those of syphilis is artificial, unnecessary, and unsupported by fact. Among other things against it are: (*a*) all animal experimentation teaches us that by the time a progressive lesion has been developed, (and certainly by the time a lesion extensive enough to produce miliary tuberculosis is present, as in the child!) the individual ordinarily has acquired resistance. That the child after infection acquires resistance promptly enough is evidenced by (*b*) the tuberculous lesions of "miniature phthisis" in early childhood, and (*c*) the fact that fibrous "disseminated tubercles" which are unquestionably usually an evidence of resistance, as we shall see, are not infrequent in childhood tuberculosis; and finally, (*d*) caseous lesions (*e.g.*, caseous pneumonia) identical with those characteristic of the child in

Ranke's assumed "hypersusceptible stage" are commonly found in adults with chronic phthisis, supposedly in the "tertiary stage" of immunity.

As for our own view, we would begin, as we have already said, with the belief that the allergic inflammatory reaction is a thing independent of some separate and as yet obscure mechanism of immunity, even though it may possibly at times support that mechanism. We have given our reasons for this belief under Section VI. In so far as we regard allergic hypersensitiveness as distinct from immunity we are in agreement with Ranke (59), Marchand (60), and Calmette (45), and run counter to the view of Rist (61), Zinsser (5), Krause (17), and Aschoff (3). Now we know from experiment that, following infection, the individual develops the ability to react allergically; and that he also develops a distinct resistance to further infection which is evidenced by a greater ability to cause the death and to restrain the growth of bacilli introduced freshly into any area, and further by the apparent tendency to "fix" the bacilli at the site at which they lodge, and so to prevent rapid spread through lymphatics; add to this the fact that a sufficient number of virulent bacilli introduced into a normal susceptible animal will spread rapidly over the body and kill it with caseous visceral lesions, and we have, it seems to us, a sufficient basis for the understanding of the differences between adult and childhood tuberculosis, without invoking any hypotheses concerning lymphatic, connective tissue, or other differences between the body of the adult and that of the child.

The way in which tuberculosis spreads in the normal animal is, in general, comparable to that in childhood tuberculosis and may be explained in the following manner: Many of the bacilli introduced locally into the normal body are well known to travel from the site of inoculation with great rapidity, indeed within a matter of minutes, as Krause and Willis, Kagayama and others have shown. Wherever these bacilli settle in different parts of the body they lodge in virgin, non-resistant soil, and in non-resistant tissues we know they can multiply with ease—so much so that it has been found that the introduction of as few as ten virulent bacilli into a normal guinea-pig may be sufficient to cause progressive, fatal tuberculosis. For a time following their introduction into the body the bacilli can multiply practically

unhampered, under conditions favorable to their growth—*i.e.*, for the length of time between infection and the development of resistance,—a period which, in the guinea-pig, after inoculation with quite large numbers of bacilli, is about two weeks. In the human being, in which infection is ordinarily initiated by relatively much smaller doses of organisms, the time required for the appearance of resistance is undoubtedly longer; but we have evidence, as we shall see, that it is certainly not a matter of years, as Ranke assumes. Now wherever the organisms have acquired a footing by multiplying unhampered where they have lodged, by the time resistance begins to appear their numbers may enter weightily into the equation necessary for the prevention of progressive tuberculosis: $R = V \times N$. Virulence is also high; and if resistance cannot rise to a level able to balance the pernicious effect of high virulence and strong numbers, the bacilli continue to live and to propagate, allergy, with its necrotizing influence, develops and a progressive lesion will occur at each such site. If one regards acquired resistance as a change in the body fluids and cells rendering them less favorable media for the growth of the bacillus, it may be asked why, then, is it that when this change finally appears during childhood infection, or in the experimental animal, the bacilli do not at once cease to proliferate and the lesions become quiescent. In answer, it may be recalled that a quite comparable situation obtains in test-tube experience with bacteria. A few bacteria implanted upon unfavorable media may all die out or fail to propagate; but progressive growth will occur on the same media if a large number of the same organisms be implanted. Likewise, bacteria which are difficult to grow (which, after all, means usually that no entirely suitable medium has yet been found) can often be cultivated with ease if large numbers are implanted together. There has been considerable discussion of this bacteriological fact. Some believe that the disintegration of organisms yields substances able to permit the growth of those remaining alive; but whatever the explanation, it seems evident that a group of many organisms can, in some way, create to a certain extent their own growth requirements in an unfavorable medium (72).

In the previously uninfected child, then, virulent bacilli reaching the lung, for example, multiply and produce the initial lesion. Many, often indeed most, of the bacilli are, however, carried promptly to the

lymph nodes and flourish in that non-resistant soil, gaining, if their numbers be sufficient, a foothold which resistance, when it at length appears, cannot destroy, and progressive extensive node lesions occur. As we have said (and as is true in any infection) fibrous tissue will fail to be prominent about the lesions in proportion to the degree of multiplication of the bacilli, the rapidity of development of allergy, the consequent rapid extension of infection and necrosis, and, therefore, the lack of a quiescent field in which repair can proceed unhampered. It is, however, only in the very rarest cases that no attempt at repair about the original lesions can be seen, and in these instances acid-fast stains show great numbers of bacilli and it is clear that caseation is progressing so rapidly and extensively that any early attempts at repair about the original lesion have become completely effaced. As for the usual failure of the more extensive pulmonary lesions in children to have the fibrous character of the chronic phthisis of adults, the common manner of pulmonary infection responsible for extensive areas of caseation in the lungs of children explains that easily, *i.e.*, the familiar sudden discharge of huge numbers of bacilli from a caseous lymph node into a bronchus. A similar aspiration of large quantities of bacilli in the adult (*e.g.* from a cavity) leads to exactly the same result. When smaller bronchial erosions occur in the child, as they commonly do in miliary tuberculosis, and fewer bacilli are discharged into alveoli, the small areas of pneumonia so produced may be encapsulated or replaced by fibrous tissue exactly as in adults. Indeed, if the material aspirated into a bronchus from a caseous node is not too heavily laden with viable bacilli, extensive fibrosis of the lung with cavity formation, identical with that seen in adults, may occur, as we shall see below (Section XV). The only other ways in which extensive, non-encapsulated pulmonary lesions can be produced in the child are (*a*) by the primary aspiration of large numbers of virulent bacilli from the outside, which then proceed to produce a progressive lesion in the non-resistant tissue; and (*b*) by the lodging of a few virulent bacilli in the lung, followed by a delay in the development of resistance sufficiently long to permit the bacilli to increase greatly in numbers before resistance appears. We know absolutely nothing about variations in the time required for resistance to appear in the human body, but it is reasonable to believe that, since numerous factors can undoubtedly

depress it after it is established, the same or other factors may interfere with its prompt development. Certainly, animals of the same species in the same experiment may vary greatly in the rapidity with which they develop, to a given degree, that other condition of altered reactivity—allergy.

This, then, is the manner in which it seems to us that the characteristics of progressive childhood infection may be explained without recourse to undue hypothesis. The character of the lesions, the extent of regional node involvement and the progress of the disease are perfectly typical of the response of the normal guinea-pig to a first infection with a sufficient quantity of virulent bacilli. When we consider that the huge caseous nodes of children are relatively enormous foci of progressive infection in proportion to the size of the body, the wonder is that extreme miliary tuberculosis is not inevitable in every case of advancing tuberculosis in childhood. We shall say more of this, however, in a moment.

Let us now consider the adult. Because of the almost universal infection of adults in civilized communities, which results from the constant exposure to the bacillus from early childhood onward, and is manifested by the quiescent tuberculous lesions found at autopsy in practically every city-dwelling adult, the adult must be regarded as comparable, immunologically, to an animal to which we have given, some time before, a primary, protective inoculation of bacilli, which has resulted in an encapsulated, localized lesion. As a consequence of this localized infection, the body of the adult, just as that of the experimental animal, is allergic, *i.e.*, the products of the bacillus produce necrosis and inflammation of its tissue more readily; it possesses acquired resistance, *i.e.*, the bacilli cannot thrive as well in it; and the bacilli appear to be held fixed wherever they lodge, so that the spread of viable organisms is delayed and greatly hampered. We have discussed this latter phenomenon above, and we have pointed out that the apparent fixation may possibly be the result of the more prompt and widespread death of bacilli in the resistant body; but since, for all practical purposes, the result is quite the same as though the bodies of the bacilli were really held fast where they lodge, until we have more information about the actual mechanism we shall speak of the phenomenon in terms of local fixation.

It is necessary to digress for a moment to consider at this point the question of the origin of adult tuberculosis—*i.e.*, whether it develops by spread of the quiescent lesions carried by practically every adult, or whether it is a result of reinfection from without. Most city-dwelling adults carry two distinct forms of quiescent pulmonary lesions from which phthisis could conceivably develop. One, the childhood primary infection, appears as an indiscriminately situated, spherical, caseous or calcified encapsulated nodule associated with similar nodules in the bronchial lymph nodes; the other type, a later lesion of reinfection, is by far most frequently situated at or near the apex (we have seen it, however, in the lower lobes as well) and appears, on section, as a spider-shaped or a plaque-like scar, often containing small foci of caseation or calcification. This latter lesion is associated with only minimal changes in the bronchial nodes—*i.e.*, minute, usually microscopic, tubercles or scars.

There is very good evidence that adult phthisis is not ordinarily an outgrowth from the original childhood infection. Opie believes, from the results of animal inoculation of primary childhood lesions, apical lesions, and apparently normal lung tissue, that the bacilli responsible for the animal tuberculosis which often follows the inoculation of primary lesions removed from adults' lungs really come, not from the lesions themselves, but from surrounding normal lung tissue. He thinks that the bacilli of the "primary complex" of childhood die out before adult life is reached. Whether or not the primary lesions of childhood actually become entirely sterile with the passage of years, there are definite pathological reasons for agreeing with Opie that adult pulmonary tuberculosis does not ordinarily represent a flare-up of the original childhood lesion. In the first place, since adult phthisis is characteristically apical in location, while the primary focus of childhood is as frequently in one part of the lung as in another, it seems clear that adult tuberculosis cannot be said to arise out of the childhood focus unless one chooses to believe that the bacilli of primary infections remain alive only in those lesions which happen to be situated at the apex. Furthermore, if the bacilli of the childhood lesions remain alive in sufficient numbers to cause the pulmonary tuberculosis of adults, the bronchial nodes of adults should show extensive involvement when the lung does, for they are as heavily infected in childhood

as is the lung—indeed, it is stated by Ranke that the nodes associated with the primary infection usually contain lesions which total twelve times the mass of the lung focus. The bronchial nodes associated with adult phthisis, however, are remarkable for the slight amount of infection which they show. Finally, it is common to find the undisturbed, quiescent, encapsulated lesion, typical of the childhood primary focus, in one of the lungs of adults with chronic apical phthisis.

What, now, of the fibrous apical lesions as the possible origin of adult phthisis? Anyone who is familiar with autopsy material must know that there exists every grade of transition from the freshly forming apical lesion to the fibrous scar on the one hand and to progressive phthisis on the other. There is no question but that the apical lesions of adults may progress to outspoken phthisis. It is further perfectly clear that these apical lesions are themselves the results of reinfection. Their fibrous nature together with the insignificant involvement of the regional lymph nodes are clear manifestations of acquired resistance; and besides, one may find a fresh apical lesion of this type in the process of formation in one lung, a distinctly older one in the other, and somewhere else in the lungs the still older, quite different primary nodule representing the childhood infection. The question as to the endogenous or exogenous origin of adult progressive phthisis is inseparable, therefore, from the question whether the bacilli of the ordinarily quiescent apical lesion came from without or from within the body. At present the question cannot be answered satisfactorily. These lesions may conceivably be the results of haematogenous metastases from an earlier lesion somewhere else in the body; or they may result from inhalation of fresh bacilli from without. We shall not enter into speculations regarding these possibilities, for more work must be done before anything of value can be said. As to the conditions under which the transition from a quiescent apical lesion into active phthisis occurs, the lesion must, in the first place, contain a relatively large number of bacilli if spread is ever to take place, for even the almost completely unresistant child is able to hold a few bacilli in check. In the second place, in spite of our inability to define the mechanism of resistance at present, we know well from clinical observation that a sufficiently large number of virulent bacilli harbored anywhere in the body will begin to grow and to produce progressive lesions if resistance becomes insuffi-

cient to hold them in check; and we know that resistance to tuberculosis unquestionably does diminish under the influence of certain diseases, of pregnancy and of less clearly definable circumstances. On the other hand, while small numbers of bacilli introduced from without are relatively harmless to the individual with good acquired resistance, (as we have repeatedly observed, in common with others, in experimental animals), large numbers of bacilli, even in the face of resistance, will grow and produce progressive lesions. Since, however, sudden massive doses acquired from without in adult life must be uncommon, we believe that tuberculosis developing in adult life practically always owes its inception to a temporary period of lowered acquired resistance, which permits the development of progressive infection from without from smaller doses, or else the extension of a focus already within the body. Which of these processes is the more frequent we cannot say with any degree of certainty.

There is, however, very good evidence that acquired resistance, although it undoubtedly fluctuates, very rarely disappears completely once the primary infection has established it. Certainly the entirety of the mass of experimental work upon the matter supports this supposition thoroughly, but in the absence of a specific test for resistance other than the introduction of virulent bacilli, the truth of it applied to the human being cannot be investigated in any way other than by the comparison of the lesions in human beings with those occuring in animals with and without acquired resistance; and such studies lead unfailingly, we believe, to that conclusion. The quiescent apical lesions of adults, often multiple and of different ages, are themselves indicators of this fact. Like fossil remains which enable us to reconstruct the environmental conditions of successive epochs, the character of these quiescent and obsolete lesions is clear evidence of the presence of acquired resistance at different and unselected periods throughout the life of the adult. Again, rarely in city-dwelling adults one finds progressive tuberculosis with little repair, associated with large caseous lymph nodes resembling those found in children. We have seen a few such cases, one of them particularly striking in that the extensive rapidly progressing lesion was situated in the lower lobe of one of the lungs. It is possible that these cases are the result of the persistence of unusually large numbers of living bacilli in both the pulmonary and

node lesions of the childhood "primary complex," with subsequent growth of the organisms in the lungs and nodes during a period of lowered resisance; or it is possible that the situation represents a fresh infection from without in a previously uninfected individual, or in one in whom resistance, if it ever existed, had been completely lost. That such cases are rare is, for reasons given above, a strong support of the idea that the bacilli of the primary complex do not commonly survive to adult life in numbers large enough to serve as the origin of adult phthisis; but their infrequency is also strong evidence that resistance, once acquired in childhood, is rarely completely lost; for were it completely lost, the adult would be reduced to the condition of the non-resistant child, or to that of the previously uninfected aboriginal adult, and infection would more frequently be of the type ordinarily seen in the child.

In the adult, then, bacilli residing in a focus in the lung, for example, (or introduced from without in sufficient numbers) during a period of lowered resistance are able to multiply; for it is remembered that we think of resistance as a condition of the body fluids and cells unfavorable to the life and growth of the bacillus. However, since some degree of acquired resistance is usually retained, the bacilli cannot grow as well and cannot acquire the impetus which their more rapid, immediate proliferation secures in the completely non-resistant body. Growth is more rapid than in the highly resistant body, but more slow than in the non-resistant one, there are few bacilli in the advancing margin of the lesion, tissue destruction is less rapid than in the non-resistant body, and the opportunity for the reparative process therefore greater. All of this is exactly what is seen experimentally in animals with any degree of acquired resistance, if the re-infecting dose be not too large. Furthermore, in the presence of the new, progressive infection resistance may be expected to rise again to a high level unless interfered with by antagonistic circumstances. Now from the periphery of the lesion bacilli are drained slowly in small numbers to the hilum nodes, for they tend to be "fixed," or immobilized, wherever they are spilled. We need imagine no sclerotic, obstructed lymphatics, or interposed intra-pulmonary nodes, as Krause does. Allow the occasional viable bacilli which escape the "fixing" mechanism of resistance to drain freely to the nodes; but no progressive, extensive lesions occur there as

in the case of the child for the reason that the few bacilli reaching the nodes at any one time lodge in ground which has some resistance, and they either die and disintegrate, or else their growth is poor and a tubercle evolves about them, exactly as happens when occasional bacilli are introduced anywhere into the tissues of an animal with some degree of acquired resistance. As a matter of fact, such tubercles are numerous enough in microscopic sections of hilum nodes in adult tuberculosis.

We have studied microscopically the hilum nodes which grossly appear almost normal in cases of adult chronic phthisis with fresh tuberculous pneumonia, and we have found that the sinuses of these nodes are always filled with cells and debris freely drained from the lung, just as during ordinary pneumonia. A glance at the contents of these sinuses leaves no doubt about the openness of the pulmonary lymphatics in adult tuberculosis (Fig. 29). Tubercle bacilli, on the other hand, although stainable in great numbers in the adjacent lung tissue of the same section, are excessively rare in the nodes, and the lesions produced there are, for the most part, the microscopic foci of epithelioid cell tissue and tubercles which are to be expected as a result of the presence of few viable bacilli. Small foci of caseation in the centres of the tubercles are common enough, and when fresh, can always be shown to be associated with the presence of a focus of bacilli. The effects of resistance upon the bacilli is impressive in these nodes, for the organisms persist for so short a time that they have completely disappeared from all but the freshest of the foci of caseation.

As for the lesser tendency to miliary tuberculosis in the adult, we may say that two factors influence the development of miliary tuberculosis in any case. First, the factor of acquired resistance. Tubercle bacilli escaping in moderate numbers into the blood stream from an established focus must, ordinarily, lodge everywhere in resistant tissues. Many, most undoubtedly, will die without producing any lesion; others surviving and slowly multiplying will give rise to occasional tubercles, and even some of these will resolve because of the death of the bacilli within them. This is exactly what we have often seen happen following an injection of carefully suspended bacilli directly into the blood stream of an animal with acquired resistance; and that it happens very commonly in adults is familiar enough from the many cases in which we find a few "disseminated tubercles" in various organs

in connection with progressive tuberculosis localized anywhere in the body. The factor of resistance is exceedingly important in this connection for every individual with a progressive tuberculous focus, whether adult or child; for, as has been said, we know from blood cultures that practically all such individuals have frequent periods of bacillemia. Were it not for the prevention of growth of bacilli by resistance, the most widespread infection of all tissues would inevitably result, just as we have often observed following intravenous injections of bacilli into normal, non-resistant animals. It is clear therefore, that, since the degree of acquired resistance is known to fluctuate, if bacillemia should occur during a period of depressed resistance the bacilli could be expected to survive at the various sites at which they lodge, as they do when unhampered by resistance. Certain cases of miliary tuberculosis may, therefore, have their origin in the coincidence of bacillemia with a period of lowered resistance. Both the adult and child, however, ordinarily possess some degree of resistance at the time when significant blood-stream infection occurs, and with progressive lesions such blood-stream infection is the rule in both adult and child. The balancing factor which will determine whether no lesions in distant organs, occasional "disseminated tubercles," or frank miliary tuberculosis will result in the face of a given degree of resistance is, therefore the *degree* of blood-stream infection; for we have produced miliary tuberculosis with ease in animals with high acquired resistance by means of rather large intravenous injections of bacilli, whereas smaller doses cause merely "disseminated tubercles" or no permanent lesions whatever. Now the more rapid extension of the lesions in the child, as opposed to the more leisurely progress with peripheral repair in the adult, obviously favors more rapid and extensive infection of microscopic and larger blood vessels in the child. Indeed, nodal tuberculosis itself, with the continual streaming of lymph through infected, necrotic nodes (Fig. 18), and thence into the subclavian vein, might be expected to be a form of tuberculosis especially favorable to blood-stream infection. If it were not for the presence of some degree of acquired resistance in the child, it is inconceivable that any case in which nodes were caseating could escape the most widespread infection; and we have, in fact, repeatedly observed in children the healed "disseminated tubercles" which are recognized

as ear-marks of acquired resistance in the adult. There is evidence, however, that not infrequently tuberculosis becomes generalized in the child before a maximal degree of resistance, comparable to that of the adult, has had time to be developed.

Opie writes in the conclusion of one of his papers that "when acute miliary tuberculosis has occurred in adults, it has not been accompanied by calcified lesions within the lungs, and the pulmonary lesion in these instances, unlike the phthisis of adults, has had the characters of a first infection. These observations indicate that general dissemination occurs because the adult has not been made resistant by infection acquired during childhood" (34). Our observations are not in agreement with this. Our autopsy studies show that there is no incompatibility between calcified lesions and miliary tuberculosis. We have, furthermore, seen miliary tuberculosis supervene in cases of typical adult chronic phthisis, and in cases in which stellate apical scars enclosing flecks of caseation were present in the lungs. No matter how resistant an individual may be, the discharge of sufficient numbers of bacilli into the blood stream will produce miliary tuberculosis. However, we are quite aware that cases such as Opie mentions do occur, and we have discussed them above. Our objection is only to the use of them as a basis for a generalization about miliary tuberculosis. It may be said that Opie himself states elsewhere in his paper that "it would be rash to deny that miliary tuberculosis might occur in the presence of an old calcified lesion."

In brief, then, our attitude toward the vexed problem of the differences between progressive adult and childhood tuberculosis is as follows: In the child, bacilli lodging locally grow freely in the body without resistance; many are swept early, in viable condition, to lymph nodes, and if in sufficient numbers and of sufficient virulence, can grow unchecked and attain to numbers large enough to be too strong for resistance when it at length appears. With the development of allergy in the presence of large numbers of proliferating bacilli, progressive, caseous lesions in lymph nodes and elsewhere, advancing too rapidly to permit much repair, become prominent. Progressive lesions in almost all city-dwelling adults develop under the influence of some degree of resistance acquired through the primary and subsequent infections, and they progress more slowly because the growth

of the bacilli is retarded by this resistance. Because of the slow extension of tissue damage the opportunity for repair is greater. Viable bacilli are swept to nodes less freely because of the mechanism which, in the resistant body, apparently tends to "fix" them at their site of lodgment, and, more important, they grow there poorly because they lodge in resistant tissue; extensive nodal tuberculosis is therefore uncommon. Blood-stream infection occurs during the course of all localized progressive tuberculosis whether in adult or child. It usually, in human infection, occurs in significant degree only after there has been time for the development of some measure of acquired resistance; and, depending upon the degree of resistance and the numbers of bacilli carried to distant organs by the blood, either no permanent tubercles, sparsely scattered disseminated tubercles, or myriads of tubercles (miliary tuberculosis) will result. The first result is very rare in adult or child, for at least a few of the disseminated bacilli produce permanent tubercles in practically every case. The second result is common in both adult and child. The last result (miliary) is more common in the child because the character of the childhood lesions is more favorable to heavy blood stream infection. The explanation of the differences between adult and childhood tuberculosis lies in the events which happen in the child *before the appearance of acquired resistance.*

We shall now pass to the application of the above principles to the understanding of various types of lesions. We shall discuss here lesions of the lung, and of the meninges and serous cavities, with only passing reference to other organs; for the same general principles apply to the entire body. It must be clear from what has gone before that any simple formula which will enable one to look at the sections of the tissues from a case of tuberculosis and to say with certainty just what had happened to the individual is completely out of the question; for the lesion which we see is always the result of (*a*) the number of bacilli originally deposited at the site; (*b*) their virulence; (*c*) the length of time they have been at that particular spot; (*d*) the character of the tissue in which the bacilli lodge; (*e*) the degree of resistance (natural, individual and acquired) of the individual; and (*f*) the degree of allergy. Unfortunately, in any given case at least four of these six factors are usually undetermined. The site of lodgment, and allergy are the only ones about which we have information; and, except when

the patient has been the subject of special, day to day quantitative tests such as we have carried out to study the fluctuations of allergy, our information in regard to that state usually consists in the result of a single routine tuberculin test which, often enough, was not contemporaneous with the lesion we have before us. However, from the study of the lesions in animals in which these factors can be fairly well controlled, we do gain certain ideas which definitely help us in the interpretation of what we see in the human being; and, while we shall always fail in the attempt to understand any particular case completely, it is clear that the same is true of practically every infection, and we must be content with information which can guide us in the general direction of a proper interpretation of the lesions which come before us.

First we shall list the chief types of lesions requiring explanation, and then we shall discuss them briefly in the order in which they are listed.

XV. THE PATHOGENESIS OF LESIONS OCCURRING IN THE LUNG

I. *Encapsulated caseous or calcified nodules of primary infection.*
II. *Tubercles.*
  A. Compact, well formed ("hard" tubercles).
    1. Localized in one area of the lung.
      a. Associated with scars in latent lesions.
      b. An extensive but localized mass of tubercles.
    2. Diffusely scattered throughout both lungs.
      a. Very sparsely distributed (disseminated tubercles).
      b. Profusely distributed (miliary tuberculosis).
  B. Loosely formed with tendency to early caseation throughout ("soft" tubercles).
    1. Diffusely scattered throughout both lungs.
      a. Profusely distributed (acute caseating miliary tuberculosis).
III. *Tuberculous pneumonia.*
  A. Acute exudative.
    1. Focal small areas.
      a. Miliary pneumonia.
    2. Extensive, but localized area.
    3. Involvement of entire lobe.
  B. Proliferative.

IV. *Progressive local invasion with destruction of large areas of tissue.*
- A. Slowly progressing, with prominent fibrous tissue formation.
  - 1. In adults (chronic phthisis).
  - 2. In children.
    - a. From first infection.
    - b. From reinfection.
- B. Rapidly progressing, with little evidence of repair.
  - 1. In adults.
  - 2. In children.

I. Encapsulated caseous or calcified nodules of primary infection. These nodules, varying in size from several millimeters to one or, rarely, two centimeters in diameter, and occurring anywhere in the substance of the lung, are the characteristic remains of well resisted primary infections of childhood. They are always associated with similar nodules in the regional lymph nodes. Stainable bacilli are often present in considerable numbers in these lesions during childhood. When the infecting dose has not been too large and growth of the bacilli of the primary infection is successfully restrained by the prompt development of resistance, non-specific, connective-tissue repair takes place about the lesion, encapsulating it with a wall of fibrous tissue which eventually becomes hyalinized.

As for the manner of origin of these nodules, although Krause maintains that the primary infection always calls forth a true, proliferative nodular tubercle, and Aschoff and many Continentals claim that the primary reaction in the lung is always exudative (pneumonic) with marked tendency to caseation, we are certain from our experiments that the response to a primary pulmonary infection may be either tubercle formation or inflammatory pneumonia, depending largely upon the numbers of bacilli and the site at which they lodge. If the bacilli remain out in the alveoli, instead of localizing in the interstitial tissue, a pneumonic process, strictly speaking, will always occur; but it may, when the numbers of the bacilli are not very large, be a pneumonia in which the alveoli are filled by a leisurely formation of tubercles, instead of by an acute inflammatory exudate. This we shall discuss below. Caseation of the area is, however, contingent upon the development of allergy, and upon the presence of a sufficiently large number of bacilli. The entirety of experimental evidence

assures us that a frank caseous pneumonia is not to be expected as an immediate reaction to first infection, for it is a manifestation of allergy, and therefore of reinfection. We have searched the lungs of many infants and children in the effort to find a lesion of first infection in an early stage of development, but we have not yet been able to surprise a primary lesion before caseation had appeared. The earliest primary nodule which we have had an opportunity of studying was a small, freshly caseous mass containing many polymorphonuclear leucocytes and nuclear fragments, and surrounded by a zone of very fresh granulation tissue which consisted chiefly of sprouting capillaries and wandering mononuclear cells. Nearby were several large tubercles which were composed of plump epithelioid cells and were beginning to undergo central caseation. Aside from lesions of the same appearance in the bronchial lymph nodes, there were no other tuberculous lesions in the body. We are therefore unable to speak with certainty about the earliest appearance of these lesions in the human being, but we have no doubt that their origin obeys the general laws which govern the first reaction to the bacillus in the lung of any susceptible animal, and these we shall deal with below.

II A. Compact, well formed ("hard") tubercles. There are two distinct types of minute, nodular tuberculous lesions. One of these types is represented by the familiar tubercle, composed of concentrically arranged epithelioid cells and usually containing one or more multinuclear giant cells (Figs. 17, 19, 21). This is the solid, compact, cellular tubercle which we speak of briefly as the "hard" tubercle, in contrast to the other type composed of a loose collection of mononuclear cells which tend to suffer early death, so that even minute tubercles of this latter variety may appear as mere foci of cheesy necrosis (Fig. 22, 24). These we have termed, for convenience, "soft" tubercles, for necrosis brings about early softening of the nodule in contrast to the increasing firmness which the compact tubercle acquires through the development of reticulum and fibrous tissue. The hard tubercle may, of course, undergo tardy central caseation, and in the instances in which the central necrosis gradually spreads until a large part of the nodule is caseous it may be impossible to distinguish the end result from that of the abortively formed soft tubercle in which the more prompt necrosis may be followed by encapsulation. However, in miliary tuberculosis

the two types stand out in striking contrast. In the one case the organs are studded with well formed, typical tubercles with or without foci of necrosis in the centers; in the other case loosely arranged accumulations of cells with early necrosis of the entire mass are found throughout the tissues. In this section we have to do with tubercles of the compact variety.

II. A. 1a. Compact tubercles associated with localized areas of fibrosis are seen commonly in sections of the apical lesions of reinfection in adults. We have discussed the significance of these lesions under section XIV, and we shall return to their characteristics below (IV. A. 1). An old fibrous apical scar may have none of the microscopical characteristics of tuberculosis, but it is easily possible to find in apical lesions, in different cases, all transitions from tubercles to fibrous scars. When tubercles are found in association with these lesions they may be incorporated in scar tissue or they may form a fringe about the margins of a scar. In this latter region they may form within the lumina of adjacent alveoli, or they may extend along the alveolar septa. The presence of indolent tubercles in association with scars is the characteristic effect of relatively few bacilli acting in the face of acquired resistance, and can be produced with ease in the experimental animal by the application of those conditions.

II. A. 1b. Extensive, but localized areas of lung tissue made solid by a dense accumulation of myriads of tubercles result from the aspiration of bacilli following the erosion of a large bronchus by an adjacent caseating lesion. Under this condition we expect, ordinarily, the development of acute caseating tuberculous pneumonia; but with very low or absent allergy, or with the discharge of not too many bacilli, acute inflammation may be transient, necrosis slight, and the formation of masses of epithelioid cells and of true tubercles may proceed sluggishly out in the alveoli. We have observed such cases in the human being, in which stainable bacilli were scanty (Figs. 8, 9), and we have produced the same process in non-allergic animals by the intratracheal insufflation of bacilli (Figs. 5, 7). It is only rarely, however, that such an event follows primarily the discharge of caseous material into a bronchus; the usual result is caseous pneumonia (Fig. 6), for allergy is usually high in progressive tuberculosis, the numbers of bacilli discharged are usually large, and caseous material impregnated with

tuberculoprotein is usually discharged along with the bacilli. But even beginning as pneumonia, if the number of bacilli are not so excessive as to cause widespread caseation, true tubercle formation may subsequently rise out of the cells of the pneumonic exudate after the heat of the allergic inflammatory reaction is over, quite as one can observe in the skin or elsewhere in the experimental animal on reinfection. If the pneumonic exudate suffers caseation here and there, the necrotic foci may themselves become encapsulated, simulating neighboring true tubercles with central caseation (Fig. 9), and the whole may gradually assume the appearance of a large, often wedge-shaped area of tubercles, interlaced in later stages by a considerable meshwork of fibrous tissue. This form of lesion is at best not very frequent, and is much more common in children because of the greater frequency, in children, of caseating bronchial lymph nodes, which may perforate neighboring bronchi and discharge relatively small numbers of viable bacilli when the bronchial erosion is not large. However, we have occasionally seen smaller, irregular foci of this nature result from the aspiration of bacilli from a cavity, in the adult, although in the latter event caseous pneumonia is far more frequent, for the reasons given above.

II. A. 2a. These are the *sparsely scattered, "disseminated tubercles,"* the result of a mild bacillemia in the face of resistance, and never found, of course, in the absence of an older lesion from which the bacilli were discharged. These disseminated tubercles are usually rather old, and of variable size. They are not infrequently fibrosed and hyalinized. It is more uncommon to surprise them in the very young, fresh state—a fact which fits entirely the knowledge that they are the result of the intermittent periods of bacillemia which are known to occur during the course of chronic tuberculosis of any organ, most of the bacilli failing to thrive where they lodge because of acquired resistance, but occasionally gaining a foothold and stirring up tubercle formation. Indeed, in every case of chronic progressive tuberculosis of any organ, disseminated tubercles can be found in distant organs if searched for. The condition can be reproduced by injecting a thin suspension of bacilli into the blood stream of an animal with acquired resistance. Although many of the older tubercles may be of the same size, it by no means follows that they are of the same age; for the size to which a

tubercle will develop appears often to be "self-limited," so to speak. After reaching a moderate size, they may, in the animal with acquired resistance, remain stationary for a long time or permanently. This we have observed in experiments in which resistant animals were killed at different periods following the intravenous injection of bacilli. This is, of course, related to the limitation of growth imposed upon the contained bacilli by acquired resistance. In section XIII we have discussed the relation of these disseminated tubercles to frank miliary tuberculosis.

II. A. 2b. This is *true miliary tuberculosis*—the result of a more active blood-stream infection. We have already dealt with the general mechanism of this form of tuberculosis. However, there is one much disputed point in this connection which we must discuss here;—*i.e.*, the process of development of the compact tubercle when the bacilli reach the lung by way of the blood stream. According to older writers, the tubercle always develops interstitially in the alveolar wall. Many modern workers deny this. According to Krause and others, bacilli transported by the blood stream to the tissues in the allergic individual always call forth an allergic exudative reaction wherever they lodge; in the lung, therefore, foci of pneumonia. Huebschmann and Arnold, whose recent work has found wide recognition, maintain heatedly that the pulmonary tubercle in miliary tuberculosis always begins as a focus of pneumonia (38). The sequence of events they believe to be (*a*) exudation; (*b*) caseation; (*c*) encapsulation; and the encapsulated pneumonic process is, they believe, what one interprets as a tubercle. "Es lassen sich keine Bilder finden die einwandfrei dafür sprechen dass bei den Fällen die unter den Erscheinungen einer akuten allgemeinen Miliärtuberkulose sterben ein wesentliches Wachstum von productiven Tuberkel mit folgender zentraler Verkäsung stattfindet." We have much material bearing upon this point—normal animals and animals with allergy and acquired resistance, subjected to various intravenous doses of bacilli of different virulence, killed at intervals of hours and days following the injections; subcutaneously infected animals with spontaneous spread of bacilli to the lungs; as well as a minutely studied series of fifty human cases of miliary tuberculosis; and we can readily show that when bacilli reach the lung by way of the blood stream, in both the normal and the allergic body, the pulmonary tubercle may begin either

within the alveolar wall or out in the alveolus itself. Usually, in animals, in which the early stages can be studied, both processes can be found in the same lung. Obviously, whether the tubercle begins within the wall or out in the alveoli will depend upon the site at which the bacilli lodge permanently when they reach the lung by way of the blood stream. The extent to which exudation will attend the escape of bacilli into the alveoli is determined by the number of bacilli which leak out into the alveoli and by the degree of allergy. Thus, some of the bacilli injected intravenously find their way into the alveolar spaces in both the allergic and the normal animal, and in both one can regularly find small foci of pneumonia which, if they do not resolve, proceed to tubercle formation. These foci are, however, distinctly more prominent in the allergic animal, as we shall see. Other bacilli, lodging in the alveolar walls, stir up tubercle formation there, in both the allergic and the non-allergic animal. Finally, bacilli engulfed by phagocytes in an alveolus may be carried into the interstitial tissue and initiate tubercle formation there. The interstitial tubercles naturally encroach very early upon the neighboring alveoli, and may simply obliterate the alveoli by extension; but more commonly, a fringe of pneumonic alveoli appears about the advancing tubercle (Figs. 3, 4). The cells of this pneumonic fringe may in turn form a compact epithelioid-cell tissue which is added to the original non-exudative tubercle, and a nodule is formed as a result of a combination of a proliferative and an exudative process. This is especially prominent in the allergic animal, and may be caused by the spilling of bacilli from the interstitial tubercle into surrounding alveoli or, since bacilli are often very rare in these collateral foci, it may be at times the result of the liberation of antigen (tuberculoprotein) from the bacilli within the tubercle. In our experiments the lungs of guinea-pigs have allowed the escape of bacilli from the blood stream into the alveoli more readily than have those of rabbits. In the former animal, therefore, it has been more easy for us to produce primary pneumonic foci by intravenous injections than in the latter.

When the tubercle develops within the alveolar wall it proceeds in a manner entirely comparable to that in which it develops in the liver capillary or elsewhere in the same animal—*i.e.*, by a primary accumulation and proliferation of mononuclear cells with secondary

central necrosis. In the course of its growth it encroaches very early, of course, upon neighboring alveoli, but it does not begin necessarily out in the alveolar space. Of this there is no possible doubt, as far as animals are concerned (Fig. 19). Huebschmann and Arnold, however, have confined their observations to human cases, and we have ample evidence from our series of human cases not only to assure us that their generalization is unwarranted, but also, perhaps, to allow us to understand the reason for their conclusion. Our proof that pulmonary tubercles in the human being may begin in the interstitial tissue, as well as out in the alveoli, is supplied by a small series of cases of extremely fresh miliary tuberculosis in which the situation of young tubercles in the alveolar wall is as perfectly clear as it is in our animals. In these cases we can show instances of even as few as half a dozen epithelioid cells grouped about a giant cell situated within the alveolar wall, with tubercles of similar character and minuteness in other organs (Fig. 20). What, then, of Huebschmann and Arnold's conclusion that this is a "theoretical fiction"? It is explained in all probability by the facts that (*a*) the vast majority of cases of miliary tuberculosis observed at autopsy are too far advanced to permit analysis of the early stages; (*b*) miliary foci of pneumonia which rapidly organize into tubercles do occur, as well as interstitial tubercles, following blood-stream infection; (*c*) interstitial tubercles very commonly form in or adjacent to the walls of bronchioles in miliary tuberculosis and, eroding the bronchial wall, discharge bacilli into these channels and so produce minute foci of pneumonia in the alveolar system behind the rupture (Figs. 30, 31, 32); (*d*) most cases of miliary tuberculosis occur in children, and associated with a large proportion of them are erosions of bronchi by caseous hilum lymph nodes with resulting foci of aspiration caseous pneumonia. The two last facts add to the ease of finding minute, fresh pneumonic foci in the lungs during miliary tuberculosis. These little foci of caseous pneumonia usually become secondarily encapsulated. Being able to find so frequently and easily all stages from small, fresh pneumonic foci to the encapsulated areas of caseation, and not having encountered the very early cases necessary for the study of the interstitial origin of tubercles (they state, indeed, that none of the cases in their series were fresh enough to show the very early reaction), it is not unnatural that Huebschmann and Arnold interpreted the matter as they

did. They do not consider at all this frequency of bronchial involvement in relation to the small foci of pneumonia, and indeed we were very much surprised to find it as regularly as we did. Of the thirty-eight cases of miliary tuberculosis in which we found, besides tubercles, small foci of tuberculous pneumonia such as Huebschmann and Arnold describe as the invariable beginning of the pulmonary tubercle, we were able to demonstrate bronchial ruptures, frequently multiple, in thirty-two cases by examination of the routine sections of the lung. It is therefore clear that bronchial erosions are very frequent in cases of miliary tuberculosis (Figs. 30, 31, 32). Since it is perfectly familiar to everyone that the common result of the discharge of bacilli into a bronchus is tuberculous pneumonia, the demonstration of multiple foci of bronchial and bronchiolar rupture in lungs containing minute patches of pneumonia should make the explanation of many of the pneumonic foci perfectly clear, and dissociate this process sharply from tubercle formation following haematogenous infection. For the study of the site of origin of the pulmonary tubercle it is essential to have cases which are not advanced beyond the point at which one can find abundant minute tubercles in the liver still in the stage of "capillary plugs." Otherwise, in the lung, in which, as is well known, the tubercle develops much more rapidly, the complications of bronchiolar involvement, and of spread of interstitial infection to surrounding alveoli, may lead to misinterpretation. In summary, then, the pulmonary miliary tubercle may begin, primarily, in the alveolar wall, in the interstitial tissue, or out in the alveolus; but not every minute, encapsulated, pneumonic focus found in cases of miliary tuberculosis is to be regarded as a primary result of blood-stream infection. Many, and in some cases, most of such foci are the result of discharge of bacilli from interstitial tubercles into bronchioles; others are associated with the very common erosion of bronchi by caseating lymph-node lesions.

II. B. Here we meet that much discussed lesion—the *"soft" tubercle:* loosely formed, often poor in cells, with a tendency to early caseation—not the usual tardy caseation of the centre of a fair-sized tubercle, but necrosis, often, of even the most minute early accumulations of epithelioid cells. In our fifty human cases of miliary tuberculosis, the tubercles were of the typical "soft" variety in seven cases; there were three

cases in which they were on the borderline between the "hard" and the "soft" variety, and all transitions between the typical "soft" and the typical "hard" forms could be found in several cases.

II. B. 1a. It is here that we must enquire into *the significance of the "soft" miliary tubercle.* Our human cases show clearly that, in the lung, the soft tubercle begins as a very minute focus of pneumonia which rapidly undergoes caseation. Later, organization or tubercle formation may appear about the periphery of the little caseous mass, eventually encapsulating it. For this type, Huebschmann and Arnold's description of the sequence of events during the formation of the pulmonary tubercle (exudation, caseation, encapsulation) is accurate in every detail. In the other organs the soft tubercle begins as a loosely formed nodule composed chiefly of mononuclear cells which undergo rapid necrosis. The early necrosis may even spread a short way beyond the component cells of the nodule and involve adjacent parenchymatous cells. This can all be followed especially well in the liver (Figs. 22, 24), but in all organs the disseminated lesions offer so striking a contrast to the compact well formed tubercles with tardy central caseation seen in the usual case of miliary tuberculosis that we shall speak of miliary tuberculosis with soft tubercle formation as "acute caseating miliary tuberculosis" to distinguish it from the ordinary type. What lies at the bottom of this difference?

That strains of bacilli of different virulence are responsible for the production of the two types of lesion has been suggested, but is quite excluded by the experiments of Meyenberg (39) who inoculated animals with bacilli from each of the types and obtained identical lesions (hard tubercles) in all animals. The fact that every gradation between the extreme hard and soft variety can be found in any large series of cases of miliary tuberculosis, and, indeed, sometimes even in the same case, would itself make such in idea improbable.

In spite of much loose discussion of the matter, as far as we can find, Huebschmann and Arnold (38) are the only investigators who have seriously attempted to analyze the factors responsible for the differences between the hard and the soft tubercle. Their conclusion, drawn from the study of the human lung, is that since, as they believe, the pulmonary tubercle begins as a focus of pneumonia which later becomes encapsulated, cases with soft miliary tubercles (which, in the

lung, as we have said, appear as miliary foci of pneumonia) are merely cases of ordinary miliary tuberculosis in which the patient has died in a very early stage of the process—*i.e.*, before encapsulation had begun. They support their contention by case histories in which they purport to show that the duration of the symptoms was always shorter in the cases in which soft tubercles were found at autopsy than in those in which hard tubercles with central caseation were found. Had the patients lived longer, the tubercles would gradually have assumed the appearance of the latter type. In regard to this opinion, we believe that any conclusions are hazardous which are based upon the estimation of the age of hard miliary tubercles which, in turn, is based upon the supposed duration of clinical symptoms. The onset of this form of miliary tuberculosis is, in the vast majority of cases, notoriously insidious. The appearance of definite symptoms does not usually cöincide with the beginning of blood-stream dissemination of bacilli. There may be no signs or symptoms whatever which would lead one to make a diagnosis of miliary tuberculosis until the lungs have become extensively involved. Especially is this true in childhood. But aside from this, the theory of these investigators fails completely to explain the condition, for our series of cases shows with perfect clarity that the hard tubercle begins in the human being, as it does in the experimental animal, not as a soft tubercle but as a compact nodule of epithelioid cells which gradually increases in size and may or may not eventually undergo central caseation. The difference in the evolution of the two forms of lesion can be followed with the greatest ease in the liver, where it becomes obvious that the most striking differences consists in the rapidity of progress toward caseation (Figs. 21, 22, 23, 24). That the soft tubercle is merely a very early stage of the hard is completely out of the question, for hard tubercles without any necrosis at all can be found in all imaginable sizes from little compact nodules made up of only a few cells to quite large tubercles. Indeed, Huebschmann and Arnold themselves realize the inadequacy of their explanation, for they qualify it by stressing the fact that the degree and rapidity of early exudation, caseation and proliferation vary markedly in different cases; and we are thus left, where we began, with the reason for this variation unexplained.

Since the soft tubercle is characterized especially by early necrosis

of the nodule and since necrosis of cells exposed to the bacillus is so greatly furthered by allergy, it might be thought that the lesion merely represents the effects of the localization of bacilli in very highly allergic tissues. This is, however, an insufficient explanation. After making animals highly allergic by preliminary subcutaneous inoculation, we have injected moderate numbers of bacilli intravenously and, killing off individuals at various intervals between twenty-four hours and a month following the injection, we have carefully studied the development of the tubercles in the various organs in comparison with those developing in control animals which were injected intravenously with the same suspension of bacilli at the same time. Although the allergic animals showed a very high degree of allergy, as evidenced by necrosis and sloughing of the skin in the tuberculin tests carried out repeatedly during the experiment (animals which suffered a depression of allergy were discarded from consideration), in none of them did the tubercles produced in the organs by the intravenous injection have anything of the character of the soft variety. Necrosis of these tubercles was not more marked, nor was the cellular compactness different in any way from that in the tubercles formed in the non-allergic controls. (The differences in the degree of pneumonia will be discussed in the next section.) Thus, the existence of a high degree of allergy, alone, will not explain the soft tubercle. That this is true for the human being also, is clear from the cases of miliary tuberculosis which we have studied in which, in spite of active allergic response to small doses of tuberculin administered at frequent intervals during the course of the illness, at autopsy only fresh, hard tubercles were found.

We have already pointed out (Section X) that numbers of bacilli are of prime importance in determining necrosis in tuberculosis—that even in the face of extreme hypersensitivity more than a very few bacilli are necessary to effect tissue destruction of any appreciable degree. If we apply this fact to the problem of the soft tubercle, we are driven to the supposition that, since the hard tubercle can develop to a considerable size without necrosis in a highly allergic body, the extensive and prompt necrosis of the soft tubercle must be due to the presence of a greater number of bacilli within it. This, in fact, is the case. Staining our human material we found that bacilli were present in great numbers in soft tubercles (Fig. 27), whereas they were always so scanty

in hard ones that in many cases sections of dozens of the latter form of tubercles would be examined before one was found in which any bacilli at all were seen. Huebschmann and Arnold also noticed that the soft tubercle regularly contains many more bacilli than does the hard tubercle, but they passed this over by assuming that the bacillus multiplies rapidly in necrotic material, *i.e.*, that the large numbers of bacilli found result from, rather than cause, the focus of necrosis. Although it is perfectly familiar that many kinds of bacteria do multiply better in necrotic material, this is by no means true as a generalization when acquired immunity enters into the question. It requires only a brief study of tuberculous lesions stained for bacilli to become aware of the fact that, as a rule, bacilli tend to die out, or at least to lose their staining qualities, rather rapidly in areas of caseation. Thus, in the caseous centres of tubercles, in caseous pneumonia which is beginning to be encapsulated, or in caseous lymph nodes, stainable bacilli are very frequently quite scanty or even entirely absent, because they have been destroyed by the body's resistance mechanism. In the early stages of the process, however, when necrosis is under way, bacilli are always found in abundance, and undoubtedly are multiplying.

We have produced soft tubercles in allergic animals by the intravenous injection of suspensions of bacilli in which we allowed small clumps to remain in order to cause the localization of numbers of organisms at each site (Figs. 25, 26). Such injections usually permit the survival of only very few of the animals of a series, because of the constitutional hypersensitive effects. We have also produced the soft tubercle by injecting, intravenously, emulsified freshly caseous lymph nodes containing large numbers of bacilli, produced by the preliminary subcutaneous infection of the same animals. This reproduces, in a fashion, the sudden discharge of clumped bacilli from a caseous focus into a large vein. These experiments, together with the presence of great numbers of bacilli in the soft tubercle, as contrasted with the few in the hard form in the human being, leave no doubt that the soft tubercle is merely the result of a massive blood-stream infection in the face of high allergy. It is probable that under these circumstances allergy becomes sometimes temporarily depressed, as was the case in some of our animals; but allergy depressed by sudden desensitization may return quickly, with renewed vigor, as pointed out by Krause and

others and as we have observed in our experiments. We have been fortunate in finding, in our human material, a case of very fresh acute caseating miliary tuberculosis in which the lesions were represented by very minute cellular accumulations with necrosis, and in this case we were able to demonstrate with ease small emboli of clumped bacilli and large numbers of single bacilli in the capillaries of various organs. In this case we had caught the massive blood-stream infection *in flagrante delicto*, and the fact that minute foci of necrosis containing bacilli were present while bacilli were still circulating in large numbers in the blood shows that even in a case of undoubted eruption of a caseous focus into a large vessel, bacilli continued to be discharged from the focus over a certain period of time. Unfortunately, the case was an old one, and there is no mention in the protocol of any attempt to find the discharging focus, but unquestionably there must have been one. It is only through the rapid discharge of large numbers of bacilli into a large vessel that acute caseating miliary tuberculosis can be produced, for the gradual dissemination of single bacilli will, in the human being as in the experimental animal, cause the production of hard tubercles only, regardless of the state of allergy or resistance, and regardless of the virulence of the infecting organism. It is this type of tuberculosis, therefore, which without any question depends upon Weigert's law for its existence. It does not follow, however, that every macroscopic discharging focus of this sort will bring about acute caseating miliary tuberculosis, for such foci may discharge their bacilli only gradually, and, furthermore, most of the bacilli contained within them may have died out before the discharge occurs. Weigert himself (35) realized that these lesions are, not infrequently, very poor in bacilli.

We have said that the intravenous injection of very large numbers of bacilli into highly allergic animals brings about severe hypersensitive constitutional symptoms and even death within forty-eight hours; and we know that in the allergic human being similar results follow the absorption of tuberculin into the blood-stream. We have every reason to expect, therefore, that when great numbers of bacilli, together with caseous material saturated with tuberculoprotein, are rapidly discharged into a large vessel, the event will be heralded by an abrupt appearance of fever, malaise and prostration, *i.e.*, by an

exaggerated constitutional allergic reaction. We have not yet studied a long enough series of cases of miliary tuberculosis from this standpoint, but in six of our seven cases of acute caseating miliary tuberculosis in which a rapid discharge of bacilli from such a focus undoubtedly occurred, the clinical histories record a sudden onset of illness. The seventh case was in an infant only seven weeks old with a history of unexplained fever of indefinite onset. We shall, however, continue the study of the pathogenesis of miliary tuberculosis with acute clinical onset, and we have little doubt that such cases will be found to be associated with a sudden macroscopical intravascular discharge of a caseous lesion, as contrasted with the insidious clinical and pathological development of miliary tuberculosis not associated with such an abrupt accident. Again, however, it will not necessarily follow that the mere *presence* of discharging macroscopic vascular lesions will always precipitate miliary tuberculosis with acute symptoms. With a gradual feeding of bacilli into the circulation from such lesions no sudden constitutional symptoms are to be expected.

III. Tuberculous pneumonia appears in two histologically distinct forms, although from the standpoint of pathogenesis they cannot be so sharply separated. The most common type is the familiar exudation into the alveoli of fluid, mononuclear cells and occasional polymorphonuclears, together with the shedding of alveolar epithelium. In the other form, the alveoli become filled with compact plugs of epithelioid cells. The exudate of the former type, (which we shall for convenience call "exudative pneumonia") is much more likely to undergo caseation. Both types may be transformed into typical tubercles or replaced by connective tissue. The tubercle bacillus more rarely calls forth a form of pneumonia characterized by the purulent nature of the exudate, which is histologically indistinguishable from ordinary lobular pneumonia. Certainly such foci, in which no other bacteria can be stained, are occasionally seen in lungs containing typical tuberculous pneumonia. This is merely an unusual form of the exudative type. That a purulent exudate may be produced in the lung by the tubercle bacillus is not surprising, for purulent pleural effusions of tuberculous etiology are well recognized, and, indeed, sufficient numbers of bacilli injected into the bronchi or under the skin of allergic

animals may call forth swarms of polymorphonulcear leucocytes as an immediate reaction.

The character and distribution of the pneumonic lesion, and the ultimate fate of the exudate will depend in any case upon the effects of allergy, of resistance, of numbers of bacilli and of the route by which the bacilli reach the alveoli.

It is well known that bacilli, falling by gravity, or drawn by aspiration into alveoli below a cavity, commonly call forth the exudative type of pneumonia in those alveoli. The route here is obvious. *Will, then, the introduction of bacilli into the alveoli by way of the bronchi invariably produce this type of pneumonia, or will this reaction occur only in the allergic body?* We have carried out experiments in which different amounts of various strains of tubercle bacilli, suspended in normal saline, were introduced by way of the trachea into the lungs of allergic and non-allergic rabbits and guinea-pigs under aseptic precautions. The animals were killed at various intervals between twenty-four hours and three weeks following the injection, and the tissues were stained for tubercle bacilli and also, as a control, for ordinary bacteria. From these experiments we can say with certainty that the immediate reaction to the tubercle bacillus is identical in quality (exudation of mononuclear and polymorphonuclear cells) in both the non-allergic and the allergic lung, but in the allergic lung the exudate is more abundant, reaches its height earlier, and early necrosis is more prominent (Figs. 1, 2). Controls, in which normal saline alone was injected, showed no inflammation at the end of twenty-four hours or subsequently. Krause states that exudative reactions in general (and tuberculous pneumonia in particular) can occur only in the allergic body, and that "in controlled experiment they are never obtainable except by the reinfection of tuberculous (allergic) animals" (2). From what we have just said it is clear that we cannot subscribe to that view. Allergy is not necessary for the occurrence of exudative tuberculous pneumonia, but, if present, it intensifies the reaction greatly (Fig. 6). It is true, however, that in most human cases of tuberculous pneumonia allergy, being present, greatly intensifies the reaction and favors necrosis. Soper, Sampson and Harkins (40) have recently reported x-ray studies (no autopsies) on animals infected through the trachea with tubercle bacilli, and they, too, found that the early response to aspira-

tion of bacilli is pneumonic consolidation in normal as well as in allergic animals, but that it appears rather more promptly and more intensely in allergic ones.

At the end of two weeks and subsequently, following the intratracheal injection of moderate numbers of bacilli, animals with acquired resistance may show distinctly less pneumonia than the originally normal controls. Indeed, after small doses, the lung of the animal with acquired resistance may become almost entirely free from lesions and bacilli. Our experiments show clearly that small foci of tuberculous pneumonia can resolve as completely as do foci of ordinary lobular pneumonia. Soper and his coworkers, also, have seen the complete resolution of tuberculous pneumonia in immunized animals, during their X-ray studies, and Austrian and Willis report the same (41). This resolution is bound up with the mechanism of acquired resistance. One may regard it as certain that, when resistance is sufficient to counteract the numbers and virulence of the bacilli in any group of alveoli, the bacilli will die and resolution will occur if the alveolar walls have not been destroyed during the allergic reaction; if only a few bacilli remain alive in alveoli in which necrosis has not occurred, they will be encapsulated in the alveoli by tubercle formation as the pneumonic inflammation subsides (Fig. 8); if caseation has involved the alveolar walls, but only a few bacilli remain alive in the area, encapsulation of the caseous mass by connective tissue will occur; if no bacilli remain alive in the necrotic focus, either encapsulation or complete replacement by connective tissue will result; and, finally, if resistance is insufficient and many bacilli remain alive, the process will spread progressively to neighboring alveoli. The statement of Marchand (60) and others that caseous pneumonia is always a manifestation of poor resistance is by no means accurate; for if sufficient bacilli find their way into the alveoli of a highly allergic individual, the immediate reaction, even in the face of high resistance, will be caseous pneumonia, just as necrosis of the skin in the phenomenon of Koch occurs in highly resistant individuals. Complete resolution can be expected, then, only in those instances in which the numbers of bacilli reaching the alveoli are not sufficient to provoke too violent an allergic reaction, and in which resistance is sufficient to destroy them.

So much for exudative pneumonia produced by bacilli reaching the

lung by way of the bronchi. *Is it possible for blood-borne bacilli to produce foci of pneumonia, rather than tubercles?*

Yes. The bacilli which reach the lung by way of the blood-stream, in either the allergic or the non-allergic individual, may either lodge in the alveolar wall and produce tubercles, or they may escape here and there into alveoli and produce miliary foci of pneumonia. We have already discussed the relation of allergy and of size of dose to the occurrence and extent of such foci of pneumonia. It is important that, in every experiment in which we injected bacilli intravenously, whenever the lungs of the allergic animals showed spilling of bacilli and cells from the blood-stream into the alveoli, the lungs of the non-allergic controls of the same series showed it as well (Fig. 28). Thus, when bacilli leak from the blood-stream through the alveolar wall into the alveoli, an exudate will appear in those alveoli in either the allergic or the non-allergic body, just as happens when bacilli fall into the alveoli through the bronchiole; and the exudate in the allergic individual under these circumstances will be qualitatively identical with, but usually distinctly more prominent and more subject to necrosis than that in the non-allergic one. Miliary foci of pneumonia occur in the human being during the septicaemia of miliary tuberculosis as we have seen above. Large foci of fresh caseous pneumonia, however, are not to be expected as an immediate result of blood-stream infection of the lung, even in the allergic body, for extensive, necrotizing allergic reactions are not produced by few bacilli, and the number of bacilli shed from the blood into the alveoli at any one point is usually small. Because of the slow growth of the tubercle bacillus, a rapid spread and confluence of originally minute, scattered tuberculous pneumonic lesions, comparable to that familiar in confluent lobular pneumonia produced by the more rapidly proliferating pyogenic bacteria, is quite unknown. That even massive blood-stream infection in the human being does not produce extensive areas of tuberculous pneumonia is clear from the minute size of the foci found in acute caseous miliary tuberculosis following the discharge of great numbers of bacilli into a vein. Even in the more chronic and thorough haematogenous seeding of the lung with bacilli, often seen in extreme degree in the generalized tuberculosis of childhood where the lungs may be uniformly riddled with caseous patches of various ages, these patches are rarely over five

millimetres in diameter and are usually rather spherical and discrete and are partially or completely encapsulated. Areas of fresh caseous pneumonia of any extent are not produced in the human being in any other way than by the discharge of bacilli or bacillary products directly into alveoli from older foci in communication with bronchi, for only in this way can large numbers of bacilli reach a large area suddenly. We have never failed to find a discharging focus of this sort in our autopsy material when large areas of tuberculous pneumonia were present.

It may be pointed out that exudative tuberculous pneumonia may appear in alveoli into which no bacilli have found their way. If bits of caseous material containing no bacilli are discharged into a bronchus from a cavity or a caseous lymph node, a pneumonic exudate will appear in the alveoli into which the material is aspirated, for such necrotic matter is impregnated with tuberculoprotein. Likewise, a fringe of alveoli containing pneumonic exudate in which no bacilli can be found is very commonly seen about tuberculous foci. This collateral inflammation has two possible modes of origin. It may result from the diffusion of tuberculoprotein into the zone immediately surrounding the lesion, for we have produced pneumonic exudates, exactly like those resulting from the injection of bacilli, by introducing tuberculin intratracheally into allergic animals. Or the collateral pneumonia may result from the action of tuberculoprotein absorbed into the circulation from some other lesion, for it is well known that the cells immediately about a tuberculous focus are much more hypersensitive to circulating tuberculin than are any other cells in the body, and that inflammation and even necrosis occurs about tuberculous foci when sufficient amounts of tuberculoprotein are absorbed into the blood-stream.

Briefly to summarize the relations of the acute exudative type of tuberculous pneumonia, we may say that:

III. A1. Disseminated small foci of pneumonia can result from infection of the lung by way of either the blood-stream or the bronchi. Irregularly scattered foci of varying size in one or in both lungs indicate aspiration from a bronchial erosion produced by an older local lesion (cavity, caseous lymph node). It is not infrequently necessary to search the lungs carefully, by making many thin sections, in order to find small cavities from which the aspiration of bacilli has occurred.

More evenly distributed pneumonic foci studding both lungs result from blood-stream infection. This is the so-called "miliary pneumonia" (III. A. 1a), and it is especially striking in fresh form in cases of acute caseating miliary tuberculosis. Any individual minute focus of pneumonia found in association with ordinary miliary tuberculosis may be either a direct result of the escape of bacilli from the blood into the alveoli or else the result of the discharge of bacilli into bronchioles from miliary tubercles involving their walls (Figs. 30, 31, 32). The erosion of large bronchi by progressive lesions is common in association with miliary tuberculosis, especially in children, and scattered foci of pneumonia from this source are frequently added to those arising from infection by way of the blood-stream and the smaller bronchioles.

III. A2. An extensive, but localized, area of pneumonia in one lung is, in the child, an exceedingly common result of the discharge of caseous material into a large bronchus following its erosion by an adjacent caseous lymph node. Bacilli are aspirated into the alveoli connected with the ramifications of the eroded bronchus, and consequently a rather sharply outlined area of consolidation results, which often has the shape of a wedge, with the base beneath the pleura. Widespread caseation of the exudate and of the lung tissue usually occurs in the consolidated area, for the number of bacilli aspirated during evacuation of the caseous node is usually large, and allergy high. When caseous material is lost by way of the bronchi from the centre of the consolidated mass, cavities are left within it, but this does not always occur. The infection may spread progressively to the lung substance about the area of immediate consolidation or, when the bacilli are held in check by resistance, resolution of exudate in the marginal alveoli, unaffected by caseation, will occur and the remaining caseous mass will become encapsulated by connective tissue. A large area of caseous pneumonia may also result from (*a*) the progressive spread of a primary infection initiated by large numbers of bacilli, or (*b*), a delay in the appearance of resistance following primary infection with smaller numbers of bacilli, such as we have discussed in section XIV. If the primary lesion in its early advance involves the wall of a bronchus, when caseation appears, as it always does, rapid spread of bacilli by way of the bronchus may occur, with a resulting area of pneumonia involving especially the alveoli associated with the eroded bronchus.

In the adult, less exposed to the danger of erosion of bronchi by caseous lymph nodes, large areas of pneumonia are practically always the result of aspiration of bacilli from a cavity in communication with a large bronchus.

III. A3. The acute pneumonic involvement of an entire lobe may result from the discharge of a caseous hilum lymph node into a main bronchus, as we have had occasion to observe in children. In adults, massive aspiration from an apical cavity may, of course, have the same effect. The slow growth of tubercle bacilli makes it highly improbable that the occurrence of acute tuberculous lobar pneumonia depends in any way upon any such obscure factors as those which determine that lobar rather than lobular pneumonia will follow infection with the pneumococcus in a given case. In order to appear rapidly throughout an entire lobe, tubercle bacilli must be actually deposited from the start throughout that lobe. We have not had many opportunities to dissect carefully cases of tuberculous lobar pneumonia but in all of those which we have studied, discharge of bacilli into bronchi leading to the involved lobes was obvious. A more gradual lobar consolidation may, of course, result from the continual aspiration of smaller numbers of bacilli from superior lesions, over a period of time.

III. B. A word now concerning *the "proliferative" type of tuberculous pneumonia*, in which alveoli become filled with solid plugs of epithelioid cells which form a coherent tissue like that of the tubercle, as contrasted with the loose inflammatory exudate seen in the ordinary tuberculous pneumonia (Fig. 8). The resemblance between this cellular proliferation and true tubercle formation is more than superficial. The process actually represents tubercle formation proceeding out into the lumen of the alveolus, forming, instead of a spherical nodule, a cast of the alveolar tree. Certainly, the same factors which favor tubercle formation favor the development of this form of pneumonia. Since we have seen that, as a general principle, large numbers of bacilli and a high allergic state favor the exudative type of reaction with early necrosis, and that the reverse conditions favor the proliferative type of reaction with the formation of a coherent tissue and a tendency to fibrosis, we may expect the proliferative type of pneumonia (*a*) in cases in which relatively few bacilli reach, and remain in, the alveoli; (*b*) in those in which allergy is low or absent; and (*c*) in those in which

a very few bacilli are left in the alveoli after a mild allergic inflammation has run its course (exudative pneumonia), since it is well known that a tubercle will develop at the site of an allergic reaction if a few living bacilli remain after the allergic outburst. We have had no difficulty in producing the proliferative type of pneumonia experimentally under these conditions (Figs. 5, 7).

IV. A1. In section XIV we have discussed at length the general principles underlying the *chronic phthisis of adults*, and it is not our purpose here to describe in detail the variations in the character of this condition in different cases. We shall, however, recall that the pulmonary lesions of adult life in civilized communities are almost invariably lesions of reinfection, whether exogenous or endogenous in origin, and that they begin as a rule, for reasons which are not yet clear, at or near the apex of the lung. What the character of the immediate reaction to the deposition of the bacilli is we cannot describe from actual observation because we have never found the lesion in such an early stage of its development, but we may be quite sure that the nature of the immediate reaction will depend upon the principles which we have formulated above in regard to the balance between the degree of allergy and the numbers of organisms deposited. Since the apical lesions develop under the influence of some degree of acquired resistance, and since they are practically never the result of sudden massive infection (section XIV), it is not surprising that they very soon show evidence of fibrosis. The youngest apical lesion which we have observed consisted in a small caseous area several millimeters in diameter surrounded by a thin zone of vascular connective tissue with a bordering fringe of fresh tubercles partly included in the connective-tissue capsule, but also extending outward radially along the framework of the lung. Shadows of alveolar walls were visible in the little caseous area, suggesting that the lesion had begun as a focus of pneumonia. There was no active tuberculosis in the body. It is this type of lesion which forms the point of departure toward complete healing (obsolete apical scar) on the one hand, or toward progressive chronic phthisis on the other. All transitions between these two extremes can be found in different cases.

We have said that the presence of indolent tubercles in association with scars is the characteristic effect of relatively few bacilli acting in

the face of acquired resistance. With the ultimate death of the contained bacilli, these tubercles may themselves become replaced by fibrous tissue, and this process is commonly seen in lesions which are undergoing transformation into the familiar obsolete apical scar. On the other hand, when larger numbers of bacilli are present in the advancing margins of such lesions, neighboring alveoli will contain a pneumonic exudate characteristic of the allergic effect of the escape of a larger number of bacilli, or the diffusion of a larger amount of tuberculoprotein into the alveoli. This is commonly seen about apical lesions which are spreading progressively toward manifest phthisis. The pneumonic exudate and the surrounding alveolar walls may or may not undergo caseation. The degree to which that event will occur hangs upon the balance between the numbers of bacilli and the degree of allergy. In progressive apical lesions caseation does usually occur to some extent, and the caseated areas produced here and there commonly become encapsulated and are left behind the advancing margin, embedded in fibrous tissue. Slowly progressing lesions of this sort may reach a very considerable size while retaining throughout the character of scar tissue with embedded foci of caseation and tubercles, with an advancing margin composed of a fringe of alveoli containing fresh and organizing tuberculous pneumonia and tubercles. When a caseating focus in the advancing margin of such lesions involves by chance the wall of a bronchiole, the opportunity for more widespread extension of damage is greatly favored by the discharge of bacilli into the air channel. When the wall of a larger bronchus is involved in this manner, the evacuation of the necrotic material provides the condition necessary for the beginning of a cavity which, depending upon the numbers and virulence of the bacilli, and the degree of allergy and of acquired resistance, may remain quite minute or may become very large through progressive destruction of the reparative attempts about it. We have discussed in section XIV the factors involved in the fluctuations in the rapidity of progress of chronic phthisis.

IV. A2a. Fibrosis and cavity formation in children, from first infection. Pulmonary lesions with very prominent fibrosis and the formation of a well walled-off cavity, either quite small, or of considerable size with a network of bared blood vessels and bronchi ramifying across it, are exceptional in young children, but in our material they have been by

no means so very rare. We have seen a number of such cases in children as young as two years. In the great majority of cases lesions of this character have resulted from the gradual spread of a primary pulmonary infection which was unsuccessfully resisted. That this is the case is clear from the facts that (*a*) they may be found anywhere in the lung (in a recent case, for example, a lesion of this sort with a cavity 3 cm. in diameter was situated at the very base of the lung); (*b*) the lymph nodes draining the lesion show marked involvement; (*c*) minute search may fail to disclose any other primary lesion; and (*d*) there is no evidence of the origin of the condition from a discharge of bacilli from a caseous node into a bronchus. As a rule the lymph nodes at the hilum reflect the character of the chronic process within the lung. They show a great deal of caseation but they are not extremely large, and scarring and hyalinization are very prominent.

These lesions occupy a place midway between those primary lesions which promptly become well-encapsulated (I), and those which progress steadily toward extensive caseation with little evidence of peripheral repair (III. A2), and their pathogenesis can be readily understood by reference to the factors determining the latter types of lesion.

IV. A2b. Cavity formation associated with fibrosis in children may, however, also result *from reinfection* of the lung. This may occur as a result of the discharge of bacilli into a bronchus from a caseous lymph node. Depending upon the number of bacilli discharged, and the degree of allergy and resistance, such an accident may lead, as we have said, to extensive rapidly progressing caseous pneumonia on the one hand and to a small, well encapsulated nodule on the other. Between these extremes there occurs the area of massive tubercle formation with scarring which we have described (II. A1b), and also the type of lesion under discussion. In our experience, however, cavity formation with prominent fibrosis has been much more commonly the result of progression of the primary pulmonary lesion, with no evidence of bronchial involvement by caseous lymph nodes. Cases of fibrosis and cavity formation resulting from hematogenous reinfection of the lung from within, or from reinfection from without by aspiration of fresh tubercle bacilli, and corresponding to adult phthisis in the slight involvement of the regional lymph nodes, are excessively rare before adolescence.

Finally, we must mention a type of slowly progressing local invasion and destruction of large areas of lung tissue which results from the direct extension of infection from a hilum lymph node. Even very large, completely caseous lymph nodes in contact with the lung are usually quite sharply separated from the lung tissue by a fibrous capsule. Sometimes, of course, caseation strikes the capsule itself and advances through the wall of an adjacent bronchus or out into the parenchyma of the lung, spreading large numbers of bacilli and producing rapidly destructive lesions. But when smaller numbers of bacilli escape into adjacent lung tissue as a result of a more gradual capsular disintegration, instead of rapidly progressing caseating lesions, foci of pneumonia appear in the alveoli immediately about the involved capsule, and the exudate becomes transformed into tubercles or organized into fibrous tissue, while any caseous foci become encapsulated. This process may be limited to a very small zone about the lymph node, or, if the numbers of bacilli are larger, the process gradually extends exactly as does a progressing apical lesion in the adult, with an advancing margin of pneumonia and tubercle formation, leaving behind scar tissue with embedded tubercles and encapsulated caseous foci. We have seen such a lesion extend from the hilum almost to the pleura, forming a dense, roughly wedge-shaped area in which the lung tissue had been practically entirely replaced by the process. In principle the advance of this form of lesion is entirely comparable to that of a progressing apical lesion in adults. Both develop under the influence of resistance, and the degree to which caseation is in evidence depends upon the balance between the numbers of organisms and the degree to which allergy is developed.

IV. B. 1 and 2. Rapid destruction of large areas of tissue. In civilized adults, with the exception of the rare individuals who escape the protective infection of childhood, rapidly progressing extensive areas of destruction of lung tissue with little evidence of repair are seen only in the case of the sudden discharge of great numbers of bacilli into the bronchi. We have discussed these lesions under III. A. 2 and A. 3. In the child, such a lesion may result from the rapid progressive spread of a primary pulmonary lesion initiated by large numbers of bacilli, or even by smaller numbers in the event of an unusual delay in the appearance of resistance following infection. We have pointed out in

section XIV that, since various infections and metabolic disturbances are well known to depress acquired resistance greatly, the accidental presence of any of these conditions immediately following a primary infection with the tubercle bacillus must hinder the prompt and successful development of resistance, and may so favor the progressive spread of an infection caused by a number of bacilli which would have been held in check had resistance developed properly. In our experience, however, very extensive rapidly progressing caseating lesions in the child are most frequently the result of the discharge of quantities of bacilli into a large bronchus from an adjacent caseating lymph node (III. A. 2).

XVI. THE PATHOGENESIS OF LESIONS OCCURRING IN THE MENINGES

I. Focal disseminated tubercles.
II. Localized caseous plaques.
III. Exudative meningitis.
  a. Diffuse.
  b. Localized.
IV. Proliferative meningitis.
  a. Diffuse.
  b. Localized.

The application of the principles set forth in this paper has been especially illuminating in the matter of the pathogenesis of diffuse exudative tuberculous meningitis. This lesion is characterized, macroscopically, by the presence of a thick gelatinous exudate in the meshes of the pia-arachnoid, especially about the base of the brain, with very minute cheesy nodules which are most abundant along the course of the blood vessels. Microscopically, the characteristic features are the abundant sero-fibrinous and cellular (predominantly mononuclear) exudate, the infiltration of the walls of blood vessels with mononuclear cells, and the necrosis of the exudate and of the infected vessel walls (Fig. 33). All of this typifies the exudative-necrotic, allergic form of reaction. In acute cases no sign of a proliferative process may be found but, since tuberculous meningitis frequently runs a course protracted enough to allow proliferative and reparative attempts to become evident following the acute allergic inflammation, sheets of epithelioid and connective-tissue cells are often enough seen

adjacent to the membranes, about the blood vessels, or encapsulating necrotic debris, and true nodular tubercles may also be found.

Because of the exudative-necrotic character of the acute reaction, and because of the frequency of the association of meningitis with miliary tuberculosis, this lesion is quite generally regarded as a prompt, allergic manifestation resulting from the localization of blood-borne bacilli in the meshes of the pia-arachnoid. According to the principles which we have discussed in this paper, extensive allergic reactions with necrosis occur only in the presence of large numbers of bacilli, and it behooves us, therefore, to enquire whether circulating bacilli actually do tend to lodge in the meninges in large numbers, or to escape from the blood vessels into the subarachnoid space. Against the belief that they do is the fact that it is not infrequent to encounter cases of miliary tuberculosis of extreme degree in allergic individuals in which every susceptible organ is riddled with tubercles, but in which there is no diffuse meningitis at all. It was these cases which first caused us to doubt that tuberculous meningitis is merely a part of generalized miliary tuberculosis, for it is unknown in tuberculosis that any tissue highly susceptible to infection by way of the blood stream is ever spared during a severe septicaemia which heavily infects all of the other susceptible tissues. Furthermore, a careful study of our cases of miliary tuberculosis associated with meningitis convinced us that the age of miliary tubercles in the viscera bears no constant relation to the age or character of the meningitis. Minute fresh miliary tubercles in the viscera may be present by the side of an old organizing meningitis, or large miliary tubercles with central caseation may be found in the viscera in cases in which the meninges show only the very freshest exudation. This speaks strongly against the contemporaneous origin of the lesions in the viscera and in the meninges. Finally, it is common enough to encounter tuberculous meningitis in cases in which no miliary tuberculosis is present and in which no large solitary tubercles are found in the brain.

Approaching the matter experimentally we found that we were completely unable to produce diffuse meningitis by either single or by repeated intravascular injections of large amounts of virulent tubercle bacilli,—not even when the bacilli were injected directly into the carotid artery. The viscera of such animals would become riddled

with tubercles, but in the central nervous system we found only scattered tubercles in the brain substance and, more rarely, in the meninges. This has been the experience of each one of the several investigators who have tried to produce tuberculous meningitis by intravascular injections of bacilli. Since the previous investigators, not concerned with the allergic nature of the reaction, had used only normal animals in their experiments, we carried out a large number of intravascular injections in allergic animals, but with quite as completely negative results as far as the production of diffuse exudative meningitis was concerned. Blood-borne tubercle bacilli do not lodge readily in the meninges or escape from the blood-stream in large numbers into the subarachnoid space. Indeed, the degree of localization of tubercle bacilli in the various tissues after intravascular injection follows closely that of inert particulate matter, and Brickner (62) has shown that only a very slight amount of injected particulate matter settles out in the meninges. Certainly, the factors of high allergy plus the presence of abundant circulating bacilli are not sufficient in themselves to bring about exudative tuberculous meningitis in rabbits and guinea-pigs. We have, however, in common with several other investigators, regularly produced quite typical exudative meningitis in these animals by injecting tubercle bacilli directly into the subarachnoid space (Fig. 33). It is worthy of recall that, as long ago as 1898, Péron (63) wrote after unsuccessful attempts to produce diffuse meningitis by injecting tubercle bacilli directly into the carotid artery: "On ne peut réproduire la méningite tuberculeuse que par l'injection de liquides virulents dans la cavité arachnoïdienne." It is curious that this fact has never been applied to the pathogenesis of tuberculous meningitis in the human being, and that this lesion continues to be regarded as the result of direct heavy infection of the meninges by bacilli escaping freely from the blood-stream.

Since, experimentally, the direct injection of bacilli into the subarachnoid space is necessary for the production of tuberculous meningitis, we set about to examine our human autopsy material for local caseous lesions in communication with the meninges, which could have served as foci of discharge of bacilli directly into the subarachnoid space. To this end the brains were cut in very thin slices, and a careful watch was kept for caseous tubercles, older than the meningitis itself, in com-

munication with the meninges or the ventricular cavities. In all we had at our disposal 40 cases of diffuse tuberculous meningitis. On careful sectioning, multiple caseous tubercles varying from several millimeters to one centimeter in diameter were found scattered in the brain substance in 38 of the 40 brains examined. In the two instances in which no such foci were found we did not have the entire brain for examination. Of these 40 cases with meningitis, 7 were free from generalized miliary tuberculosis, but even in these one or more caseous tubercles were found in the brain, undoubtedly a result of the haematogenous dissemination of bacilli which always occurs in association with a progressive lesion anywhere in the body. We have, in this connection, examined the brains from six cases of pulmonary tuberculosis without meningitis, in which disseminated tubercles were found in the abdominal viscera, and in every instance we found caseous tubercles in the substance of the brain. It is thus quite clear that disseminated tubercles in the brain are frequent complications of progressive visceral tuberculosis.

We have, then, in these caseous foci in the substance of the brain, a potential source of discharge of bacilli directly into the subarachnoid space. It is necessary only that, in their growth, they reach the meninges without encapsulation, or else discharge into the ventricular system; and this is exactly what we have found in 33 of the 40 cases of meningitis which we have studied. In 31 of these cases, caseous tubercles, usually multiple, were found in the cortex extending to the surface of the brain (usually in the depths of a sulcus) and directly infecting the meninges (Fig. 35). In two cases, caseous tubercles discharged directly into the ventricles. These tubercles within the brain substance do not, however, exhaust the possibilities of direct meningeal infection. We found in our animal experiments that following bloodstream infection occasional tubercles would form in the meninges themselves; and on careful scrutiny of the meninges in cases of miliary or disseminated tuberculosis without diffuse meningitis in the human being, we found frequently a few scattered, circumscribed tubercles in the pia-arachnoid (Fig. 34). Now just as the bacilli lodging in the substance of the brain may, under the proper conditions of dosage, virulence and resistance, proliferate and give rise to circumscribed caseous tubercles of considerable size, so may those lodging in the

meninges; and the result of such an event is a sharply circumscribed caseous mass varying from several millimeters to several centimeters in diameter, situated in the meninges either on the surface of the brain or hidden within a sulcus. On the surface of the brain the mass tends to assume a plaque-like form. These caseous foci may be encapsulated and remain quiescent. We have found them in the complete absence of diffuse meningitis. If, however, they begin to spread progressively at a rate which allows the escape of bacilli into the surrounding meninges, diffuse exudative meningitis follows, beginning first in a zone immediately about the focus but rapidly spreading to involve the meninges everywhere as the bacilli discharged from the focus are distributed throughout the subarachnoid space. Of our 40 cases of meningitis two were caused directly by the escape of bacilli into the subarachnoid space from such caseous meningeal foci. One of these cases was particularly interesting in that the diffuse exudative-necrotic meningitis began during the puerperium in the complete absence of miliary tuberculosis or of any other progressive lesion elsewhere in the body. The meningitis was easily traceable to a large old caseous meningeal lesion deep in a sulcus, and clearly represented a flare up of this old lesion during the period of lowered resistance associated with the puerperium. The caseous focus itself was undoubtedly the result of a period of bacillemia some time before, either during the childhood primary infection or during the later apical reinfections, and it is entirely comparable to the large solitary tubercles within the brain which may remain stationary in size for a long time or, increasing in size during a period of lowered resistance, give rise to pressure symptoms.

Finally, one of our forty cases of meningitis was the result of the direct extension of a tuberculous process from an infected vertebra to the subarachnoid space.

Thus by careful search we have been able to discover older local caseous foci in communication with the meninges in 36 out of 40 cases of tuberculous meningitis. We have little doubt that they were present in the four cases in which we did not find them, for aside from the fact that in two of these four cases we found multiple caseous foci in the brain not in communication with the meninges, in none of these cases was the whole brain available for examination. Furthermore, in none of these four cases were we able to study the spinal cord, and we have

several times found caseous tubercles in the cord in other cases.[7] It is, besides, quite an easy matter to miss small caseous tubercles in the brain in any gross method of search, for slices cut free hand are, unless made with the most painstaking care, often thicker than the diameter of the tubercles. The thorough search of the entire brain for caseous foci in communication with the sub-arachnoid space is a tedious and time-consuming affair, although not infrequently the striking abundance of meningeal exudate in a particular area gives a hint that a discharging lesion will be found in the brain beneath.

It is hardly necessary to say that not every brain tubercle which extends to the meninges produces diffuse exudative meningitis. This complication depends upon the character of the tubercle—*i.e.*, upon whether or not bacilli are readily discharged from its margins. Obviously, a tubercle in which encapsulation keeps pace with growth may reach the meninges without discharging more than an insignificant number of bacilli, which produce only a small area of meningitis immediately about the tubercle. Likewise, of course, a bronchus or a blood vessel may be eroded by a similar tubercle without the precipitation of widespread pneumonia or the appreciable dissemination of bacilli throughout the body. Indeed, widespread exudative meningitis occurs rather rarely as a result of the presence of very large tubercles in the brain, even when they are in contact with the meninges, for it is very uncommon for these tubercles to reach a diameter of several centimeters before becoming encapsulated. The foci responsible for meningeal infection are, rather, the smaller caseous tubercles with little or no encapsulation which have their origin in the gray or white matter near the surface of the brain.

The characteristic and prominent involvement of the meningeal blood vessels in exudative tuberculous meningitis has led to the belief that the bacilli, arriving by way of the blood-stream, reach the meningeal spaces by penetrating the vessel walls, and this is frequently offered in support of the idea that tuberculous meningitis is a direct and immediate result of the septicaemia of miliary tuberculosis.

[7] The middle ears were not available for study in these cases; and it should be pointed out that tuberculous otitis media may involve the meninges by extension of the process through the bone.

Against such a view is the pertinent fact that careful study will show that the intimal change (accumulation of cells beneath the endothelium) is regularly a later event than the adventitial infiltration. But we have more definite evidence against the belief that this vascular involvement proves that the bacilli active in causing the meningitis are infecting the blood vessels from within. In the first place, in the experimental meningitis which we produced by injecting bacilli directly into the subarachnoid space, the vascular involvement was identical with that observed in human tuberculous meningitis, and there was just as marked a tendency for the process to localize in and about the walls of the vessels (Fig. 36); and in the second place, we have observed seven human cases in which there was no miliary tuberculosis at all, but in which there was meningitis produced by the discharge of bacilli into the meninges from caseous brain or meningeal lesions, and in all of these cases the vascular alterations were perfectly characteristic of those supposed to be proof of the blood-stream origin of tuberculous meningitis. In these human cases, as in the experimental animals, we knew the route by which the bacilli reached the meninges, and it was not by way of the blood through the vessel walls.

It is important to state finally that the bacilli responsible for the ependymal "tubercles" commonly observed in cases of tuberculous meningitis can reach the ventricles by retrograde transport from the subarachnoid space, although the movement of the cerebrospinal fluid is in the opposite direction. We have found this ventricular infection both in the animals in which we introduced the bacilli directly into the meningeal spaces, and in the human cases in which meningitis followed the discharge of bacilli into the subarachnoid space on the surface of the brain in the absence of miliary tuberculosis. Numerous investigators have shown that inert particulate matter introduced into the subarachnoid space about the brain or the spinal cord can find its way into the ventricular cavities. The infection of the ependyma, therefore, is not to be regarded as an evidence of blood-stream dissemination of bacilli.

We have in another place (6) presented and illustrated the following facts in support of the thesis that tuberculous meningitis is not a direct result of septicaemia with the tubercle bacillus, but that its existence

depends upon the presence of local lesions which discharge bacilli into the subarachnoid space:

1. Cases of extreme, generalized miliary tuberculosis without meningitis.
2. Experimental failure to produce meningitis by blood-stream infection.
3. Ease of experimental production of meningitis by direct infection of meninges.
4. Cases of meningitis without generalized miliary tuberculosis but with caseous lesions discharging bacilli directly into meninges.
5. Frequency (95 per cent) of tuberculous foci found in the brain in association with progressive visceral tuberculosis.
6. Frequency (90 per cent) of older caseous lesions discovered in communication with meninges in a total of 40 cases of tuberculous meningitis.
7. The age and character of miliary tubercles in the viscera in generalized miliary tuberculosis with meningitis bears no constant relation to the age or character of the meningitis.
8. The vascular alterations supposedly constituting evidence of arrival of bacilli by way of the blood stream occur in meningitis without miliary tuberculosis, and also follow direct experimental infection of the meninges.

We must point out that blood-stream infection can occur as a *result* of tuberculous meningitis. A cursory microscopic examination of this lesion will convince one that the walls of innumerable blood vessels are usually heavily infected, and acid-fast stains show clearly the manifold opportunities for the escape of bacilli into the blood-stream. But aside from this, at the suggestion of Dr. W. G. MacCallum we have studied the condition of the pacchionian granulations, and in several cases we have found them hanging, heavily infected, into the venous sinus—obviously a further potential source of blood-stream infection. We have seen miliary tuberculosis follow the direct experimental infection of the meninges. Austrian (65) and Manwaring (66) report the same; and infection of the meninges from a brain tubercle, in the human being, may be followed by miliary tuberculosis in the absence of any other progressive visceral tuberculosis.

XVII

What we have said of the meninges we believe to be true of *serous cavities* in general. The familiar sudden, massive pleural effusion, for example, is usually dismissed with the rather vague statement that it is

an allergic manifestation following the lodging of bacilli in the pleura, and reference is made to the work of Paterson and others who produced a similar effusion by injecting bacilli into the pleural cavities of allergic animals. But how do the bacilli reach the pleura in human cases? We believe that, without question, in each such case a local tuberculous focus must have ruptured into the serous cavity—a caseous subpleural lymph node, a focus at the surface of the lung, or a cold abscess in association with vertebral tuberculosis, discharging bacilli into the pleural cavity; a caseous focus in bone or cartilage discharging into a joint; a tuberculous Fallopian tube or caseous mesenteric lymph node discharging into the peritoneal cavity; a tuberculous lymph node involving the pericardium, or a direct extension from pleural tuberculosis. Weigert was aware of this as long ago as 1883 (67). Our reasons for believing this are (*a*) massive effusions do not occur when bacilli lodge only here and there in these membranes even in the face of allergy, as witness the absence of pleural effusion in many cases of miliary tuberculosis in which the pleura is studded with tubercles; (*b*) massive effusions do occur when a caseous focus ruptures into a serous cavity, as we have had occasion to observe at autopsy in numerous instances; (*c*) we have never been able to produce a serous effusion by intravascular injection of bacilli into normal or allergic animals; (*d*) effusion can be produced by injection of bacilli directly into a serous cavity in an allergic animal; and (*e*) small numbers of bacilli, such as might enter the pleural cavity from the blood-stream, if injected directly into the cavity fail to produce an appreciable effusion. Paterson, himself, speaks of the "enormous dosage" and the "huge masses of bacilli" which he had to inject into the pleural cavities of allergic animals in order to produce the exudative inflammation (9). It is obvious that such quantities of organisms in the human being can reach a serous cavity only through the means of a local, discharging tuberculous focus. Although a minimal exudative inflammation may follow the escape of small numbers of bacilli from the blood-stream of an allergic animal, since only small numbers ever do escape so at any one of the sites in question, we may state as a general principle that all of the outspoken, extensive, exudative tuberculous inflammations (pneumonia, meningitis, effusions into serous cavities) have a common manner of origin, *i.e.*, the discharge

of abundant bacilli from a nearby local tuberculous focus directly into the area in question.

We have desired to present in this paper an analysis of the principal factors concerned in the pathogenesis of tuberculosis, and it is not possible to summarize briefly the results of this analysis. The table of contents will, however, serve to indicate the problems investigated, and will provide a means by which direct reference may be made to any particular part of the subject in which one happens to be interested.

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PLATE 1

FIG. 1. INFLAMMATION PRODUCED BY TUBERCLE BACILLUS IN NORMAL ANIMAL

Lung of normal guinea-pig 24 hours after intratracheal injection of 2 cc. moderately heavy suspension of virulent human tubercle bacilli. Bacterial stains show no other bacteria. Polymorphonuclear and mononuclear pneumonic exudate is of same character as that in similarly treated allergic animal (Fig. 2), but is less extensive. (See pp. 281, 312, 361.)

FIG. 2. INFLAMMATION PRODUCED BY TUBERCLE BACILLUS IN ALLERGIC ANIMAL

Lung of allergic guinea-pig 24 hours after reciving same intratracheal dose of same suspension of bacilli as that given the normal pig of Fig. 1. No other bacteria present. Reaction identical in quality, but more extensive than in Figure 1. (See pp. 281, 361.)

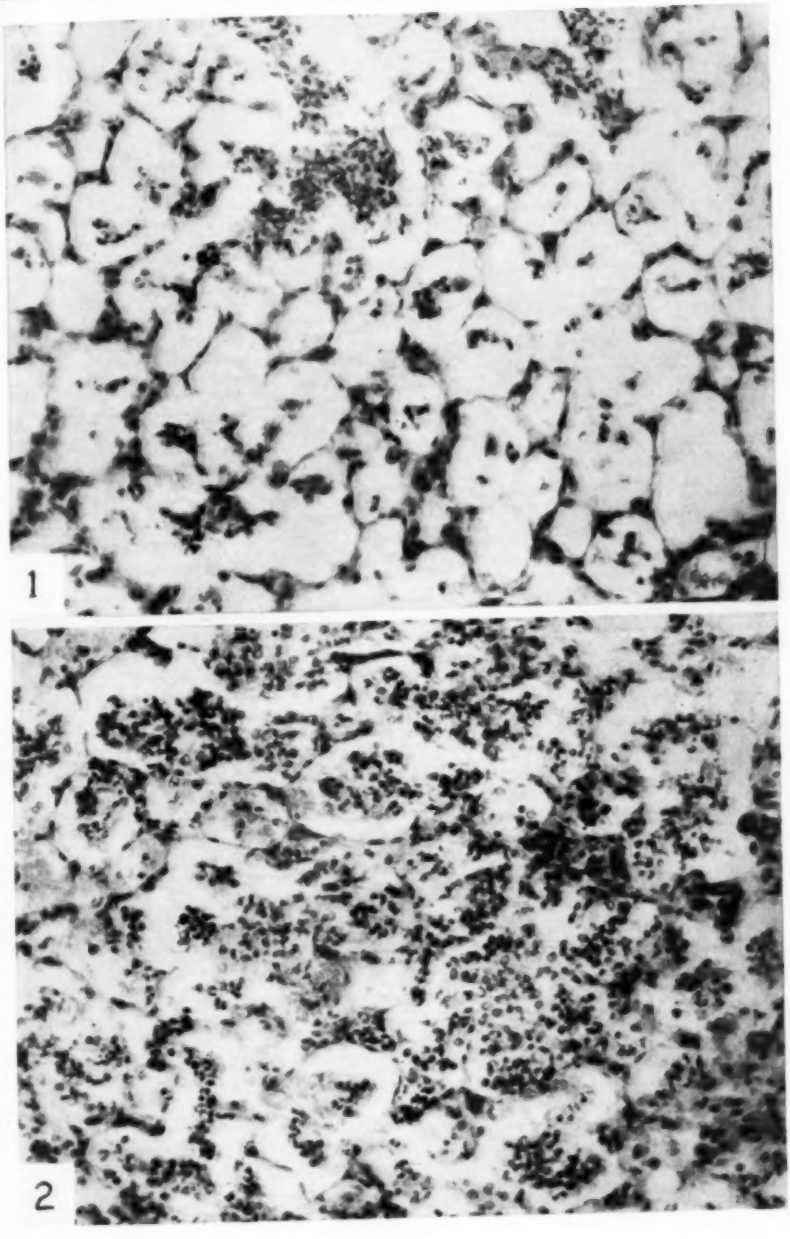

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PLATE 2

FIG. 3. COMBINATION OF INTERSTITIAL PROLIFERATIVE AND EXUDATIVE PNEUMONIC PROCESS IN FORMATION OF PULMONARY TUBERCLE

Lung of normal rabbit 3 days after intravenous injection of 3 cc. moderately heavy suspension virulent bovine bacilli. Shows an interstitial tubercle, with slight collateral pneumonic exudate in which occasional tubercle bacilli can be stained. These bacilli spilled into the alveoli will subsequently be enclosed in epithelioid-cell tissue. (See p. 352.)

FIG. 4. COMBINATION OF INTERSTITIAL PROLIFERATIVE AND EXUDATIVE PNEUMONIC PROCESSES IN FORMATION OF PULMONARY TUBERCLE.

Lung of allergic rabbit 3 days after intravenous injection of same dose, same suspension of bacilli as that given rabbit of Figure 3, shows more extensive collateral pneumonic exudate, and some necrosis. (See p. 352.)

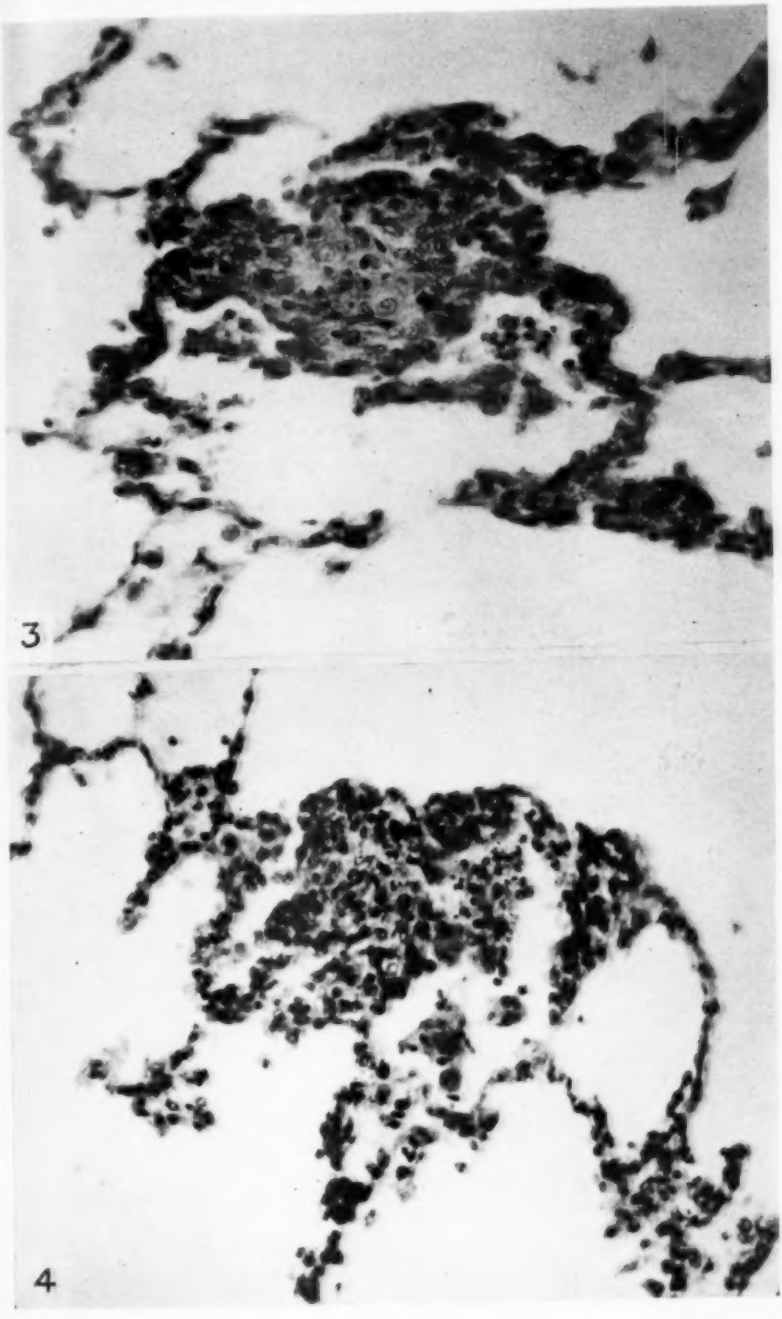

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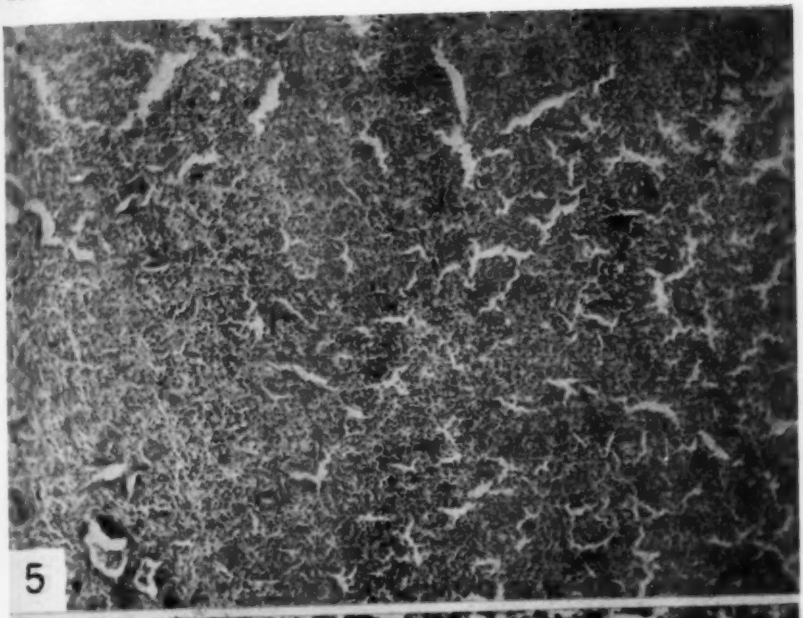
PLATE 3

FIG. 5. EXPERIMENTAL PROLIFERATIVE PNEUMONIA

Lung of normal rabbit 10 days after intratracheal injection of virulent bovine bacilli. Animals of this series killed earlier showed that the immediate mild exudative pneumonia is gradually replaced by intra-alveolar epithelioid-cell tissue shown here. Figure 7 is a higher magnification. (See pp. 349, 367.)

FIG. 6. EXPERIMENTAL CASEOUS PNEUMONIA

Lung of allergic rabbit 10 days after receiving same dose of same suspension of bacilli as that given rabbit of Figure 5. Widespread necrosis of pneumonic exudate and, in places, of alveolar walls as well. No other bacteria present. (See pp. 349, 361.)



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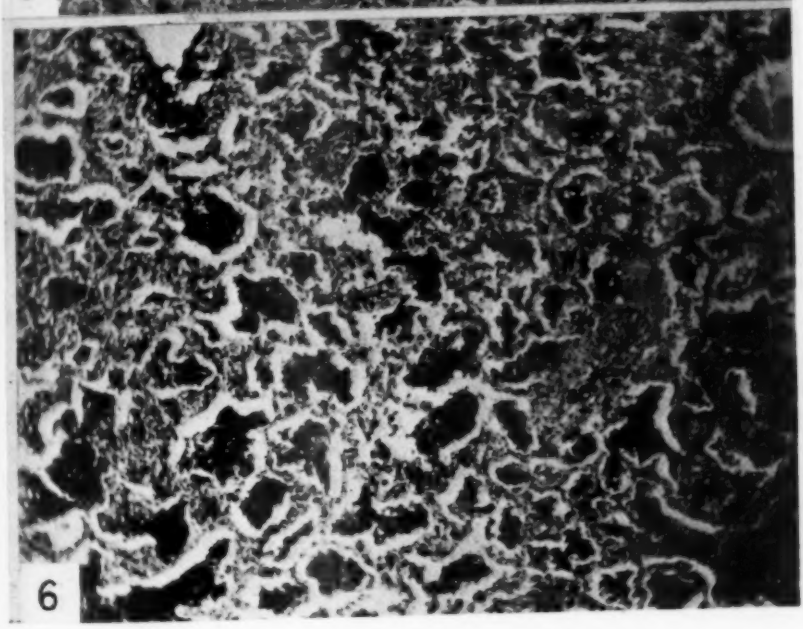

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PLATE 4

FIG. 7. HIGHER MAGNIFICATION OF FIGURE 5

(See pp. 312, 349, 367.)

FIG. 8. PROLIFERATIVE PNEUMONIA IN HUMAN LUNG

Very few stainable bacilli present. (See pp. 349, 362, 366.)

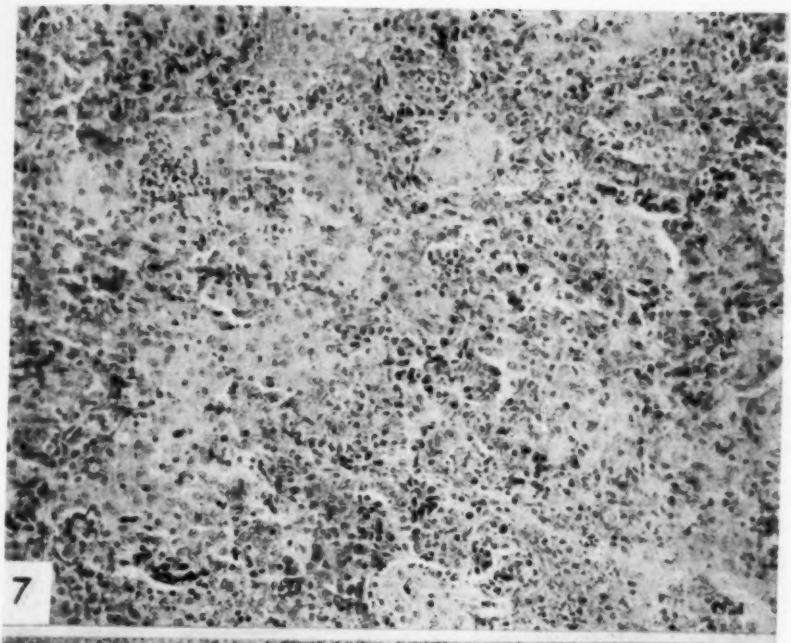

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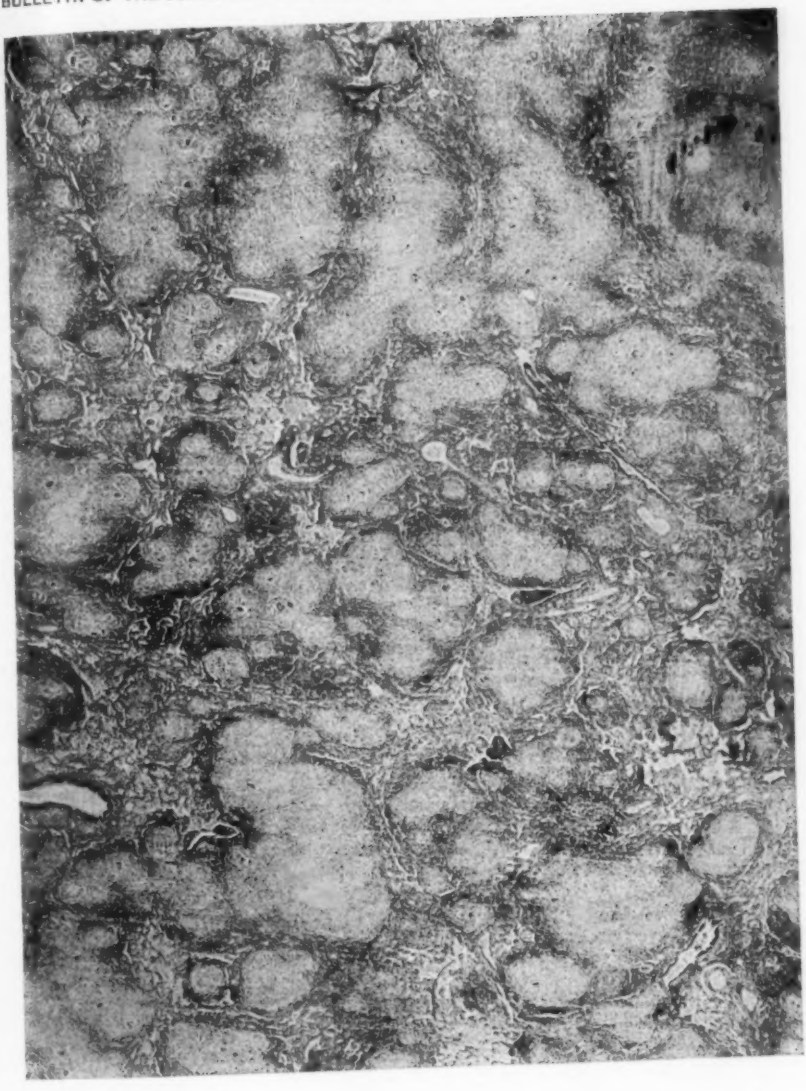
PLATE 5

FIG. 9. EXTENSIVE AREA OF DENSE TUBERCLE FORMATION IN HUMAN LUNG

Very few stainable bacilli present. (See pp. 349, 350.)



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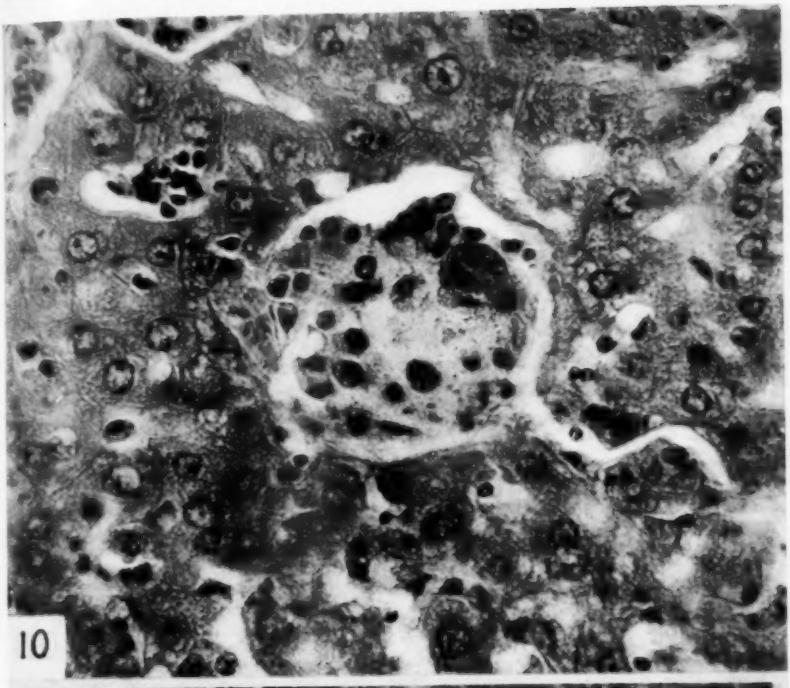
PLATES 6 AND 7

FIGS. 10, 11, 12 AND 13. DIFFERENT STAGES IN THE RESOLUTION OF TUBERCLES

Rabbit's liver. Figure 10 shows early stage of "loosening up" of cells of the tubercle. No necrosis. In Figure 11 many of the cells of the tubercle have left the spot. Figure 12 shows inflow of red corpuscles filling space left by exodus of cells of the tubercle. Two giant cells and several mononuclear cells still remain. Two other small resolving tubercles can be seen on the right, one above and one below. Figure 13 shows complete disappearance of the tubercle, the space being now occupied by fresh blood and fibrin clot. (See p. 318.)



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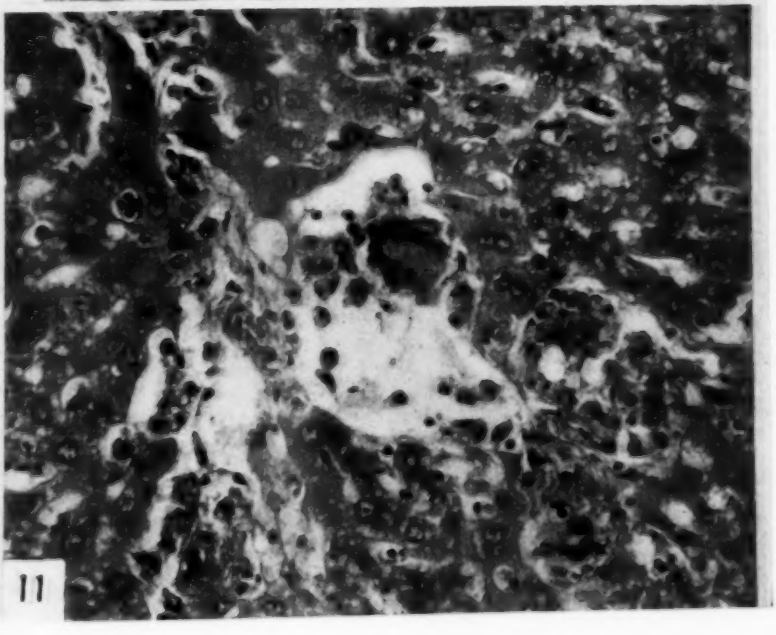

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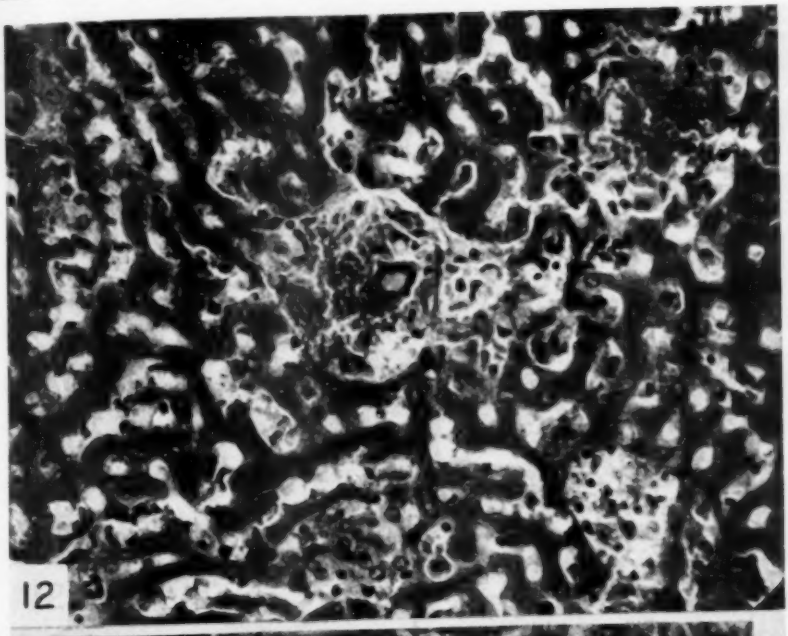

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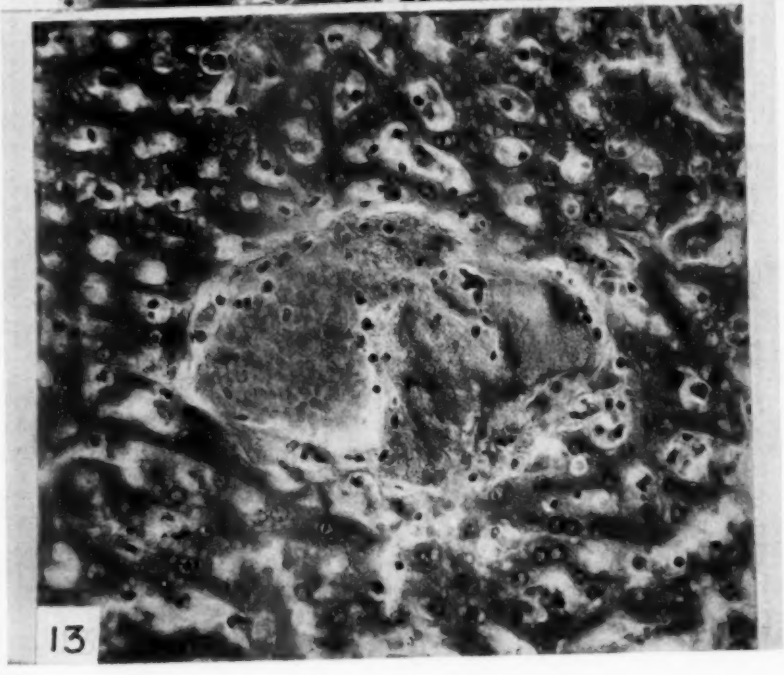

13

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PLATE 8

FIG. 14. SHOWS MANY DIFFERENT SIZES OF TUBERCLES RESULTING FROM SINGLE INTRAVENOUS INJECTION OF BACILLI; TENDENCY TO PERIVASCULAR LOCALIZATION OF TUBERCLES; INVASION OF VESSEL WALLS

Lung of normal rabbit 21 days after injection of 2 cc. of fine suspension virulent bovine bacilli into ear-vein. (See pp. 321, 322, 323.)

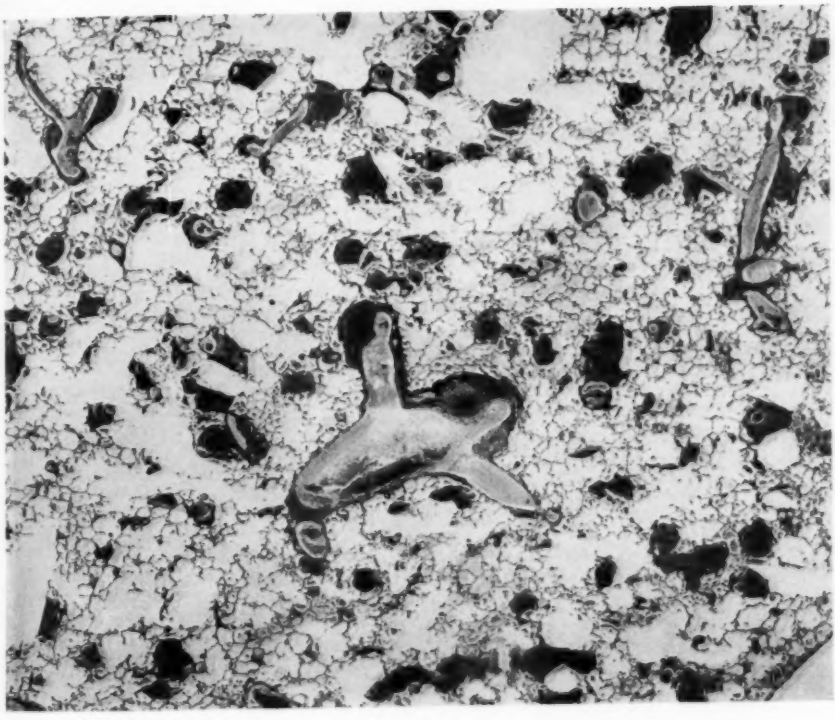

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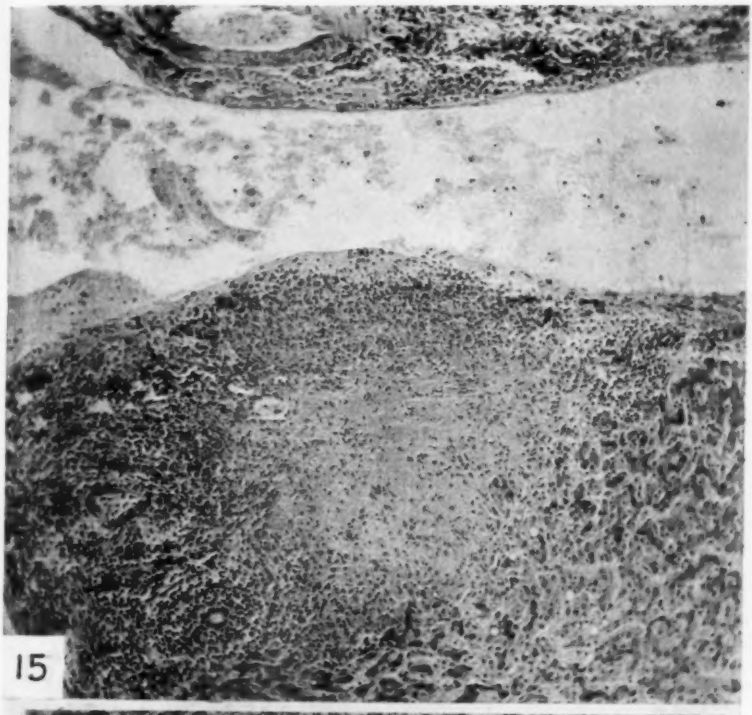
PLATE 9

FIGS. 15 AND 16. INFECTION OF BLOOD STREAM BY MILIARY TUBERCLES INVADING MINUTE BLOOD VESSELS.

Liver from human cases of miliary tuberculosis. Figure 15 shows beginning rupture of endothelium. Figure 16 shows destruction of endothelium, and acid-fast stains show bacilli being discharged into blood stream from the ragged, necrotic mass. (See pp. 321, 322, 324.)



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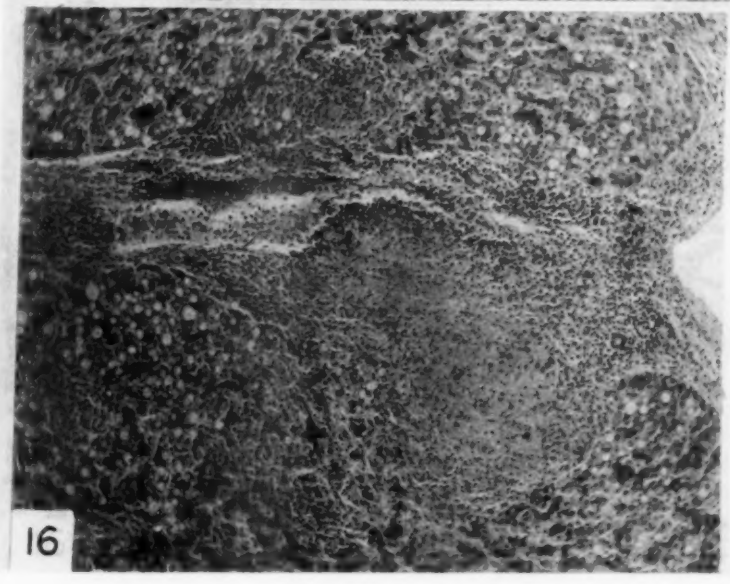

16

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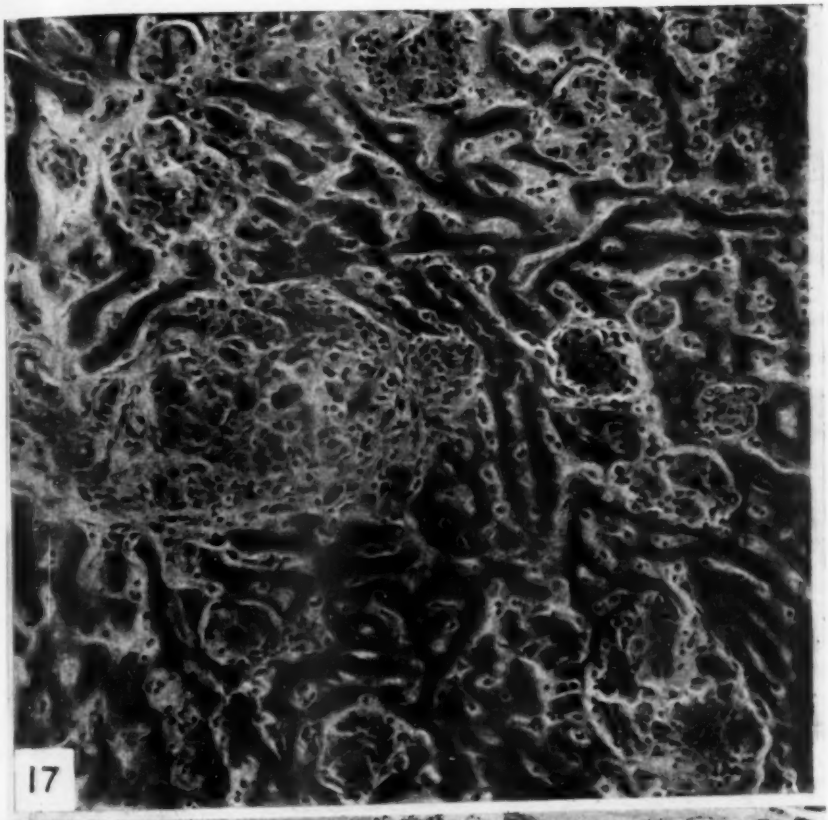
PLATE 10

FIG. 17. TUBERCLES OF DIFFERENT SIZES RESULTING FROM SINGLE INTRAVENOUS INJECTION OF BACILLI

Liver of normal rabbit 14 days after injections of 2 cc. of fine suspension virulent bovine bacilli into ear vein. (See pp. 323, 348.)

FIG. 18. INFECTION OF LYMPH STREAM WITHIN CASEOUS NODE

Bronchial lymph node from child. Acid-fast stains show discharge of bacilli into this lymph sinus from necrotic material which invades it. (See pp. 321, 343.)



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18

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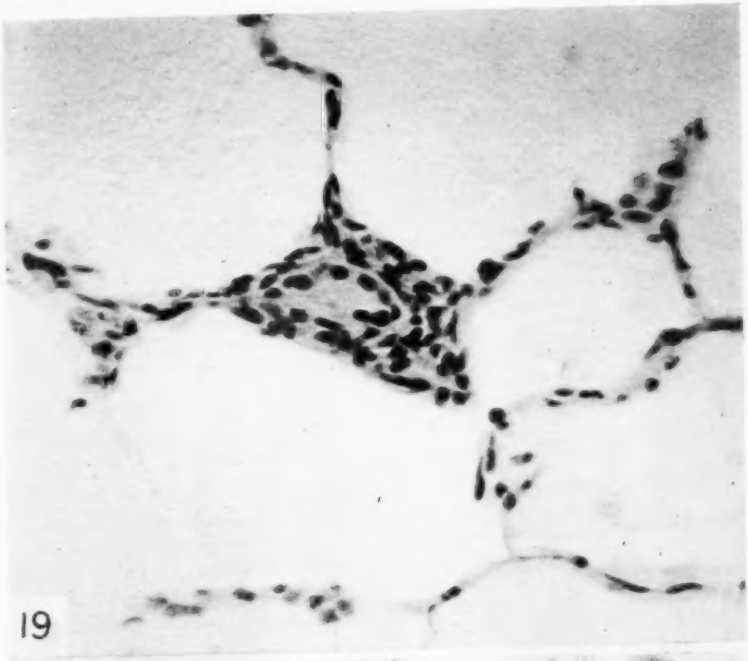
PLATE 11

FIG. 19. INTERSTITIAL TUBERCLE

Lung of normal rabbit 8 days after intravenous injection of fine suspension virulent bovine bacilli. (See pp. 348, 353.)

FIG. 20. INTERSTITIAL TUBERCLE

Human lung from case of miliary tuberculosis. (See p. 353.)



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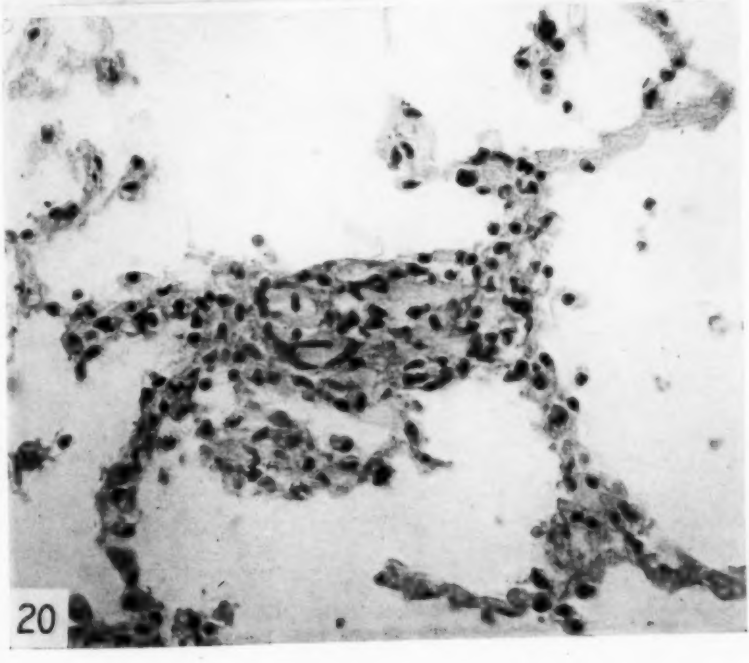

20

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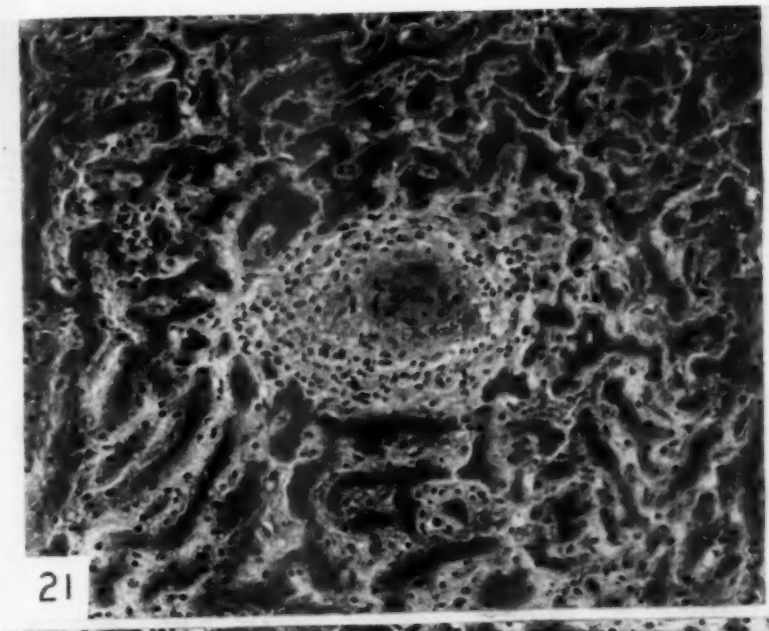
PLATE 12

FIG. 21. MINUTE "HARD" TUBERCLE

Liver from case of human miliary tuberculosis. Acid-fast stains of single sections of this type of tubercle show bacilli only very rarely. (See pp. 348, 356.)

FIG. 22. MINUTE "SOFT" TUBERCLE

Human liver from case of acute, caseating miliary tuberculosis. Stains of single sections of this type of tubercle always show many bacilli, as seen in Figure 27. (See pp. 348, 355, 356.)



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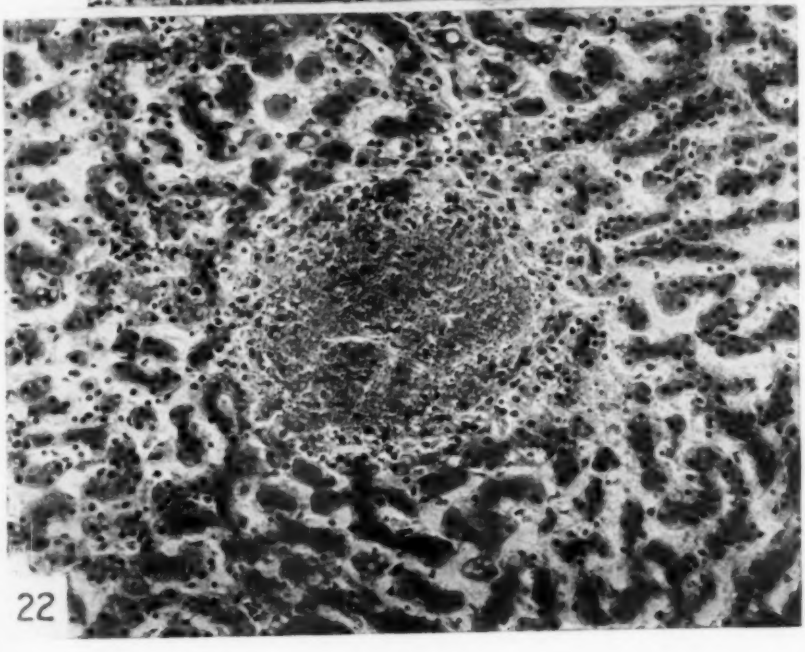

22

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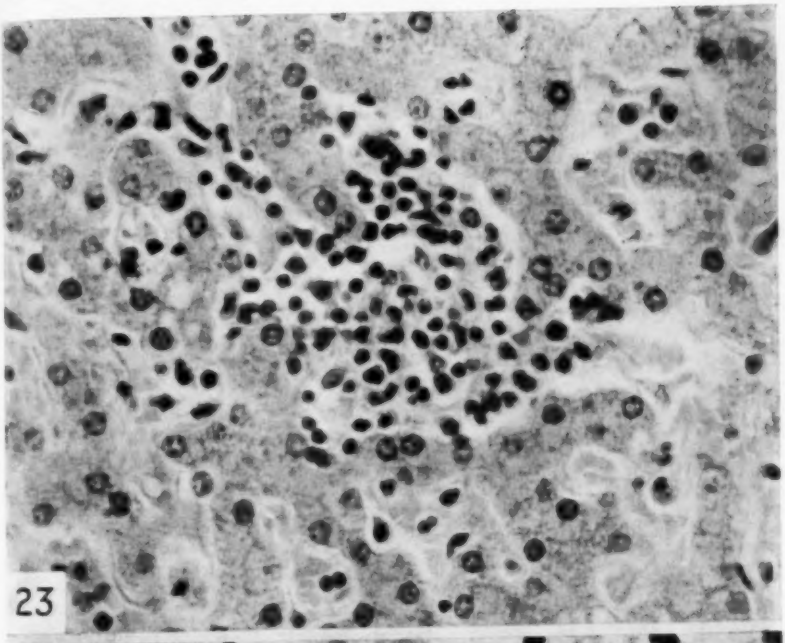
PLATE 13

FIG. 23. BEGINNING "HARD" TUBERCLE

Human liver from case of miliary tuberculosis. All cells are alive. Very rare stainable bacilli in such foci. Compare with Figure 24. (See p. 356.)

FIG. 24. BEGINNING "SOFT" TUBERCLE

Human liver from case of acute, caseating miliary tuberculosis. Many cells are dead (note karyorrhexis). Many stainable bacilli in such foci. (See pp. 348, 355, 356.)



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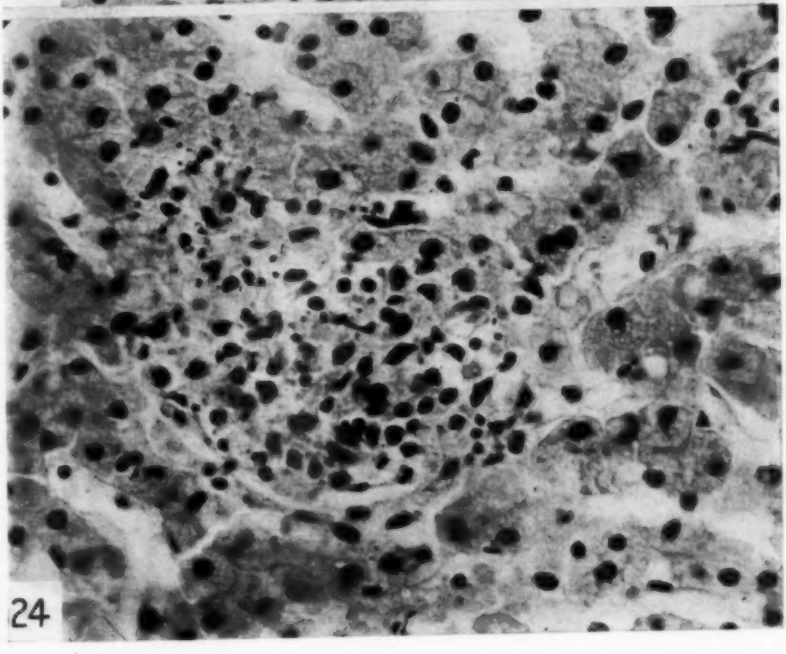

24

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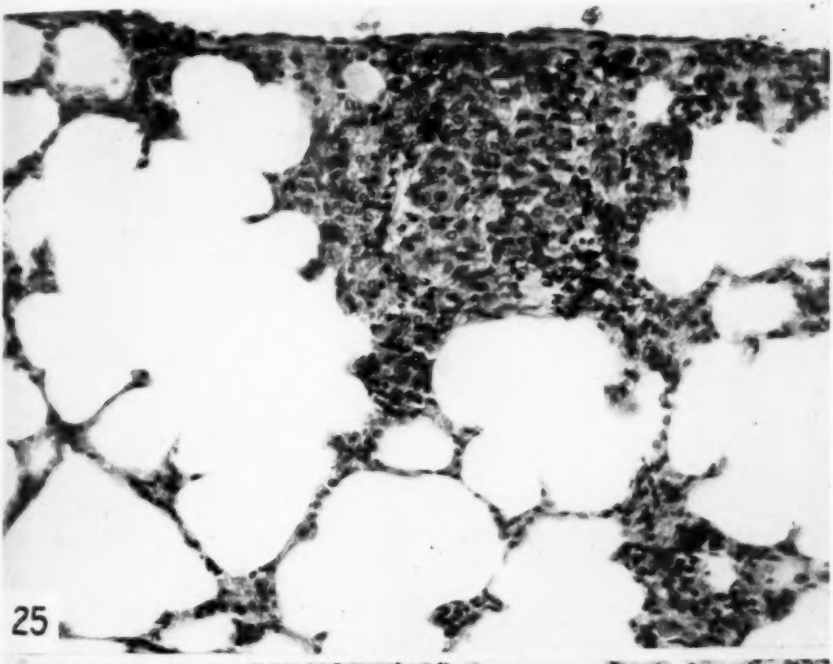
PLATE 14

FIG. 25. EXPERIMENTAL "HARD" TUBERCLE

Lung of guinea-pig, 13 days after intravenous injection of 2 cc. fine suspension virulent human bacilli into allergic animal. Acid-fast stains show very few bacilli. (See p. 358.)

FIG. 26. EXPERIMENTAL "SOFT" TUBERCLE

Lung of guinea-pig, 13 days after intravenous injection of 2 cc. heavy suspension virulent human bacilli into allergic animal. Acid-fast stains show large numbers of bacilli. (See p. 358.)



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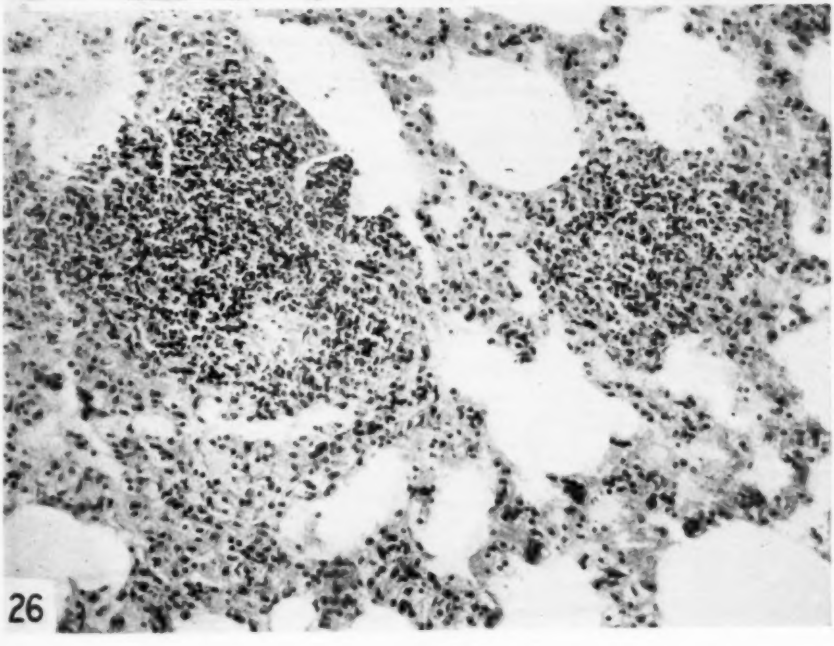

26

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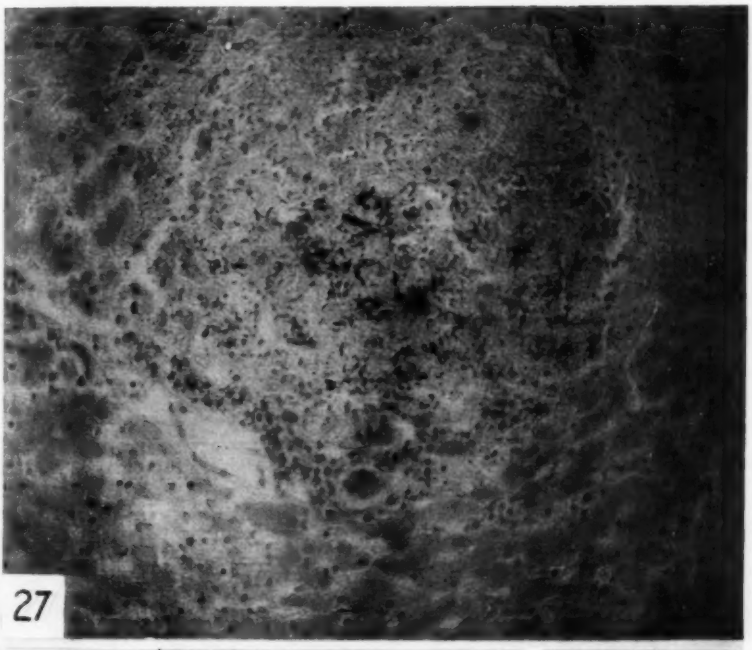
PLATE 15

FIG. 27. SHOWING THE LARGE NUMBER OF BACILLI IN A "SOFT" TUBERCLE

Human liver from case of acute, caseating miliary tuberculosis. Acid-fast stain. Black lines and clumps are bacilli. (See p. 357.)

FIG. 28. MINUTE FOCUS OF HAEMOTOGENOUS PNEUMONIA

Lung of normal rabbit 48 hours after intravenous injection of 3 cc. moderately heavy suspension virulent bovine bacilli. Stainable tubercle bacilli free in alveoli with polymorphonuclear and mononuclear exudate. No other bacteria present. (See p. 363.)



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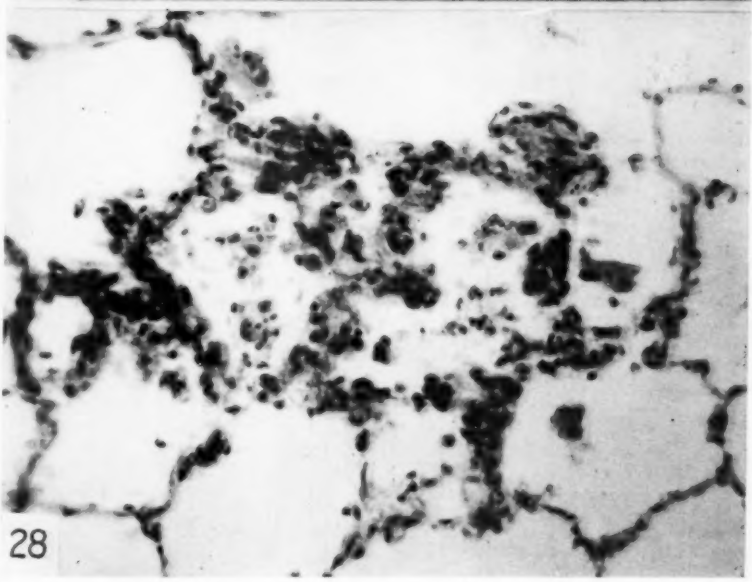

28

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PLATE 16

FIG. 29. SHOWING FREE DRAINAGE THROUGH LYMPHATICS FROM LUNG TO LYMPH NODE IN ADULT

Lymph sinus of bronchial node of adult 45 years old with active "adult type" pulmonary tuberculosis. The sinus is seen to be filled with cells and debris drained from the lung. Stainable tubercle bacilli are, however, very rare. (See pp. 330, 342.)

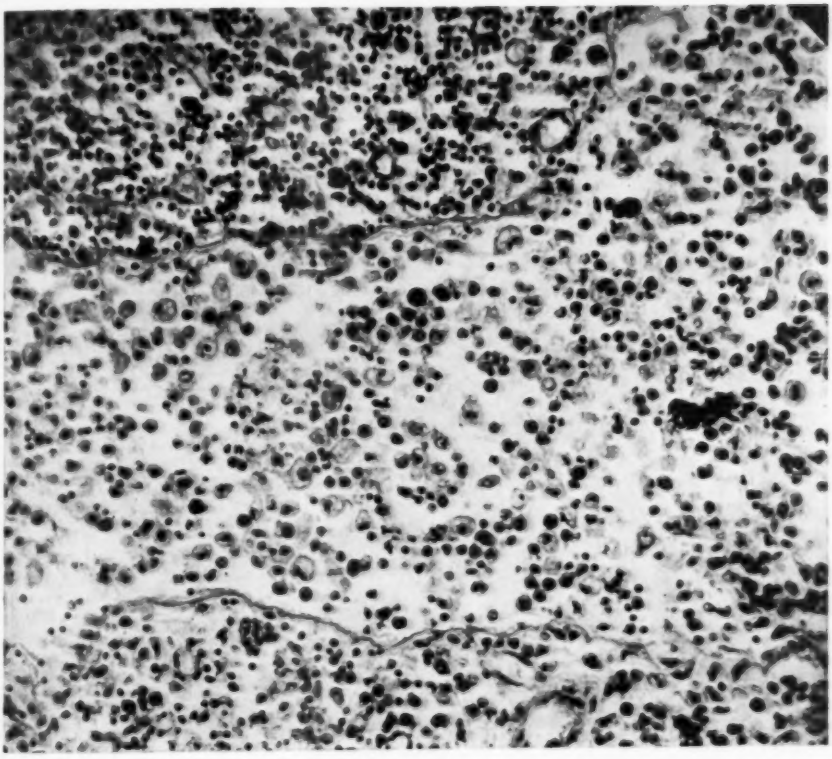

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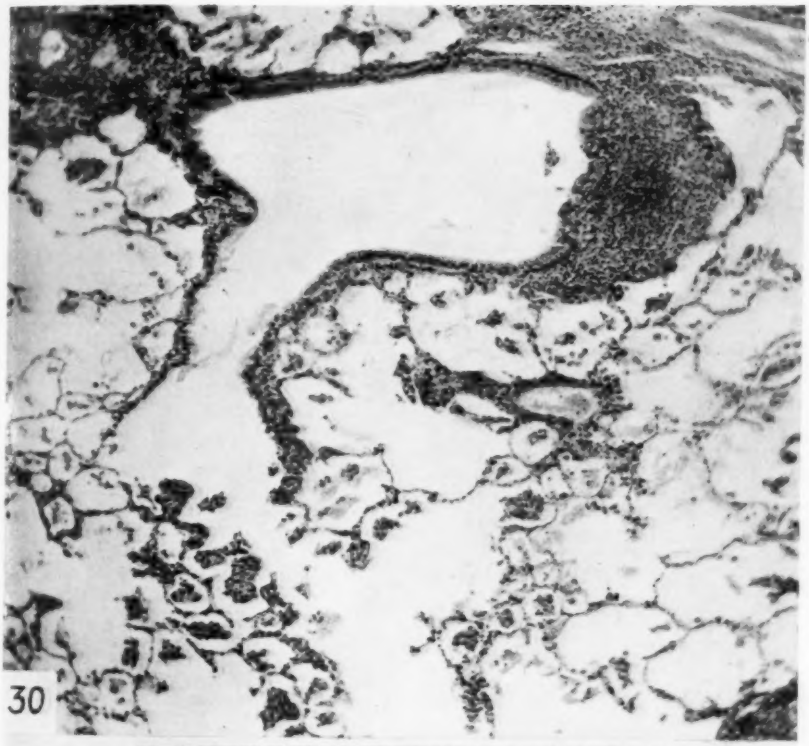
PLATE 17

FIG. 30. PNEUMONIA ARISING FROM DISCHARGE OF BACILLI INTO BRONCHIOLE FROM MILIARY TUBERCLE

Rabbit's lung 5 weeks after intravenous injection of fine suspension virulent bovine bacilli into previously normal animal. A necrotic miliary tubercle can be seen discharging into right side of bronchus. Fresh pneumonic exudate, containing bacilli, lies in the alveoli into which this bronchiole opens. No other bacteria present. (See pp. 353, 354, 365.)

FIG. 31. CASEOUS MILIARY TUBERCLE DISCHARGING INTO BRONCHIOLE

Human lung, miliary tuberculosis. (See pp. 353, 354, 365.)



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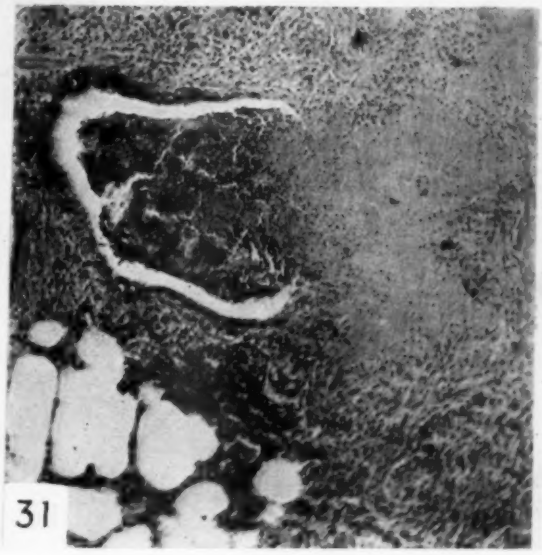

31

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PLATE 18

FIG. 32. MILIARY TUBERCLE DISCHARGING INTO BRONCHIOLE

Human lung, miliary tuberculosis. (See pp. 353, 354, 365.)

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PLATE 19

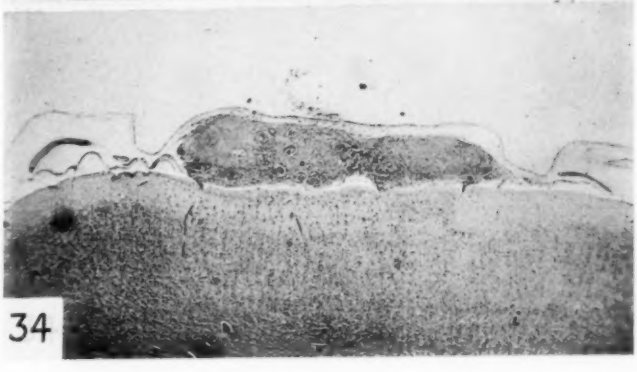
FIG. 33. EXUDATIVE MENINGITIS

Produced by injection of virulent bovine bacilli into subarachnoid space of allergic rabbit. This exhibits in all details the characteristics of human tuberculous meningitis. (See pp. 371, 373.)

FIG. 34. SMALL, SHARPLY CIRCUMSCRIBED, CONGLOMERATE MILIARY TUBERCLE IN MENINGES

From human case of extreme miliary tuberculosis in which the viscera were riddled with tubercles of the same general size and character. In the meninges, however, there were only a very few of these tubercles, and no exudative meningitis whatever. This is, likewise, the only meningeal result of intravascular injections of bacilli into animals. (See p. 374.)

33



34

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PLATE 20

FIG. 35. TYPICAL CASEOUS, CORTICAL TUBERCLE DISCHARGING INTO MENINGES AND SO PRODUCING EXUDATIVE MENINGITIS

Human brain. The exudate covered the hemisphere containing this tubercle, not yet having spread to the opposite side, and was most prominent in the meninges near the tubercle. (See p. 374.)

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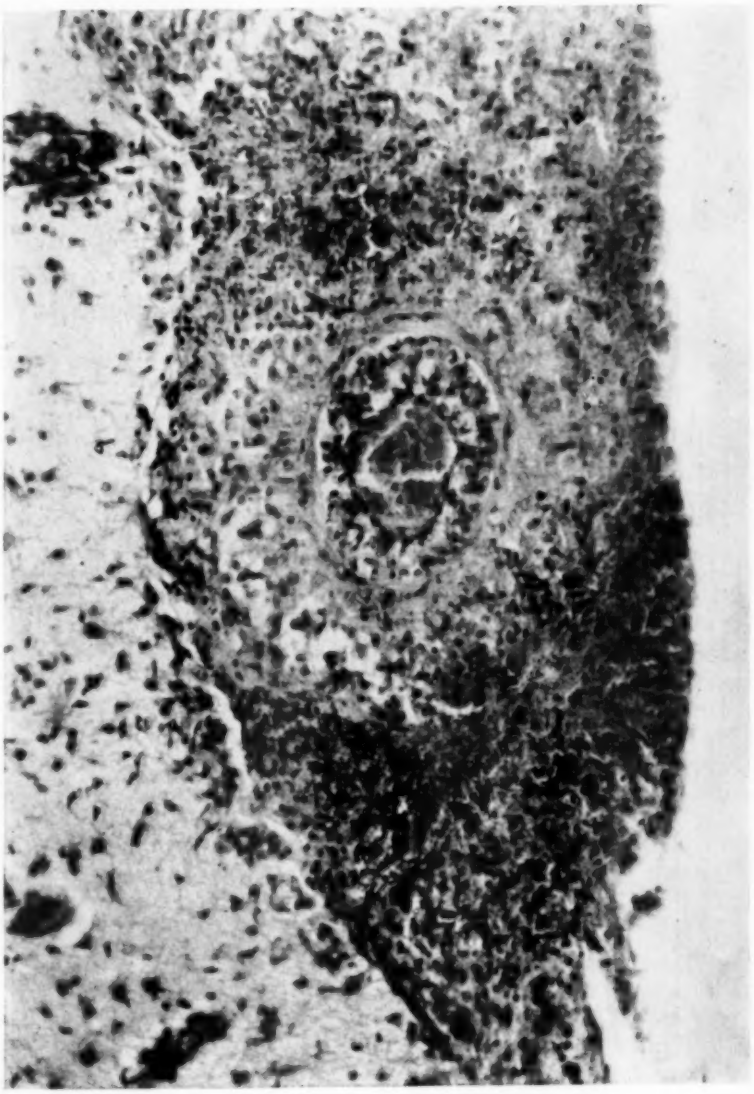
PLATE 21

FIG. 36. VASCULAR ALTERATIONS PRODUCED BY DIRECT INFECTION OF MENINGES

Rabbit. Injection of virulent bovine bacilli into subarachnoid space of allergic animal. Inflammatory cells beneath endothelium of meningeal vessel, necrosis of wall of vessel and invasion by inflammatory cells, typical of that seen in human meningitis, and erroneously regarded as evidence that bacilli responsible for meningtis reached the meninges by way of the blood stream. (See p. 377.)



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PROGRAMS OF THE MEDICAL SOCIETY OF THE JOHNS HOPKINS HOSPITAL

OCTOBER 15, 1928

1. Presentation of cases:
   a. Poliomyelitis. James Bordley, III, M.D.
   b. Post-traumatic arterio-venous fistula. Julian Hart, M.D.
2. Total extirpation of the dog's liver in one stage. W. M. Firor, M.D. and D. Stinson, M.D.
3. The problem of urinary secretion as elucidated by a study of the kidney of *lophius piscatorius*. E. K. Marshall, Jr., M.D. and A. L. Grafflin, A.B.

NOVEMBER 12, 1928

1. Presentation of cases:
   a. Pachymeningitis hemorrhagica. R. McIntosh, M.D.
   b. Syringomyelia with Morvan's disease. D. Hart, M.D.
2. The human brain in evolution. Frederick Tilney, M.D., Professor of Neurology, Columbia University.

DECEMBER 7, 1928

Acute intestinal obstruction. H. W. Carson, F.R.C.S., Senior Surgeon, Prince of Wales General Hospital, London, England.

DECEMBER 10, 1928

1. Presentation of cases:
   a. A case of congenital anophthalmos, bilateral. A. L. MacLean, M.D.
2. The racial differences as illustrated by the mydriactic action of cocaine, euphthalmine and ephedrine. K. K. Chen, M.D. and Edgar J. Poth, Ph.D.
3. Concerning certain visual field disturbances associated with hysteria, being a retrospect and the present concept. George E. de Schweinitz, M.D., LL.D., Sc.D.

JANUARY 7, 1929

1. The nature of osteitis fibrosa and giant-cell tumor. Charles F. Geschicter, M.D. and Murray M. Copeland, M.D.
2. On the nature of Ewing's sarcoma. Murray M. Copeland, M.D. and Charles F. Geschicter, M.D.
3. Discussion of the above named papers. James Ewing, M.D., Professor of Pathology, Cornell Medical School, New York.

FEBRUARY 11, 1929

1. Case reports:
   a. Bilateral pneumothorax following tracheotomy. E. N. Broyles, M.D.
2. Some common pathological conditions of the middle and inner ear that are associated with deafness. S. J. Crowe, M.D.
3. Otitis media in infants under one year of age. S. W. Egerton, M.D.
4. Current studies under the John J. Abel Fund for Research on the Common Cold. J. A. Doull M.D.

MARCH 11, 1929

1. The rôle of allergy in tuberculosis. Arnold R. Rich, M.D.
2. Moving pictures of the living developing rabbit's egg. Warren H. Lewis, M.D.

SPECIAL JOINT MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY AND THE HISTORICAL CLUB OF THE JOHNS HOPKINS HOSPITAL TO COMMEMORATE THE 300th ANNIVERSARY OF THE BIRTH OF MALPIGHI

The principal speaker of the evening was Professor Doctor Joseph Franchini, Director of the Institute of Tropical Diseases, University of Bologna, Italy. A collection of instruments, books, etc., used by Malpighi was on exhibit.

JOINT MEETING OF THE SOCIETY OF HYGIENE OF THE JOHNS HOPKINS UNIVERSITY AND THE MEDICAL SOCIETY OF THE JOHNS HOPKINS UNIVERSITY

February 20, 1929

1. The chemical nature and biological activity of the active principle of tuberculin. Dr. Florence B. Seibert, University of Chicago.
2. The tuberculin reaction as a factor in the lesions of tuberculosis. Dr. Esmond R. Long, University of Chicago.